Diagnosing skin cancer in general practice

Cecile Koelink

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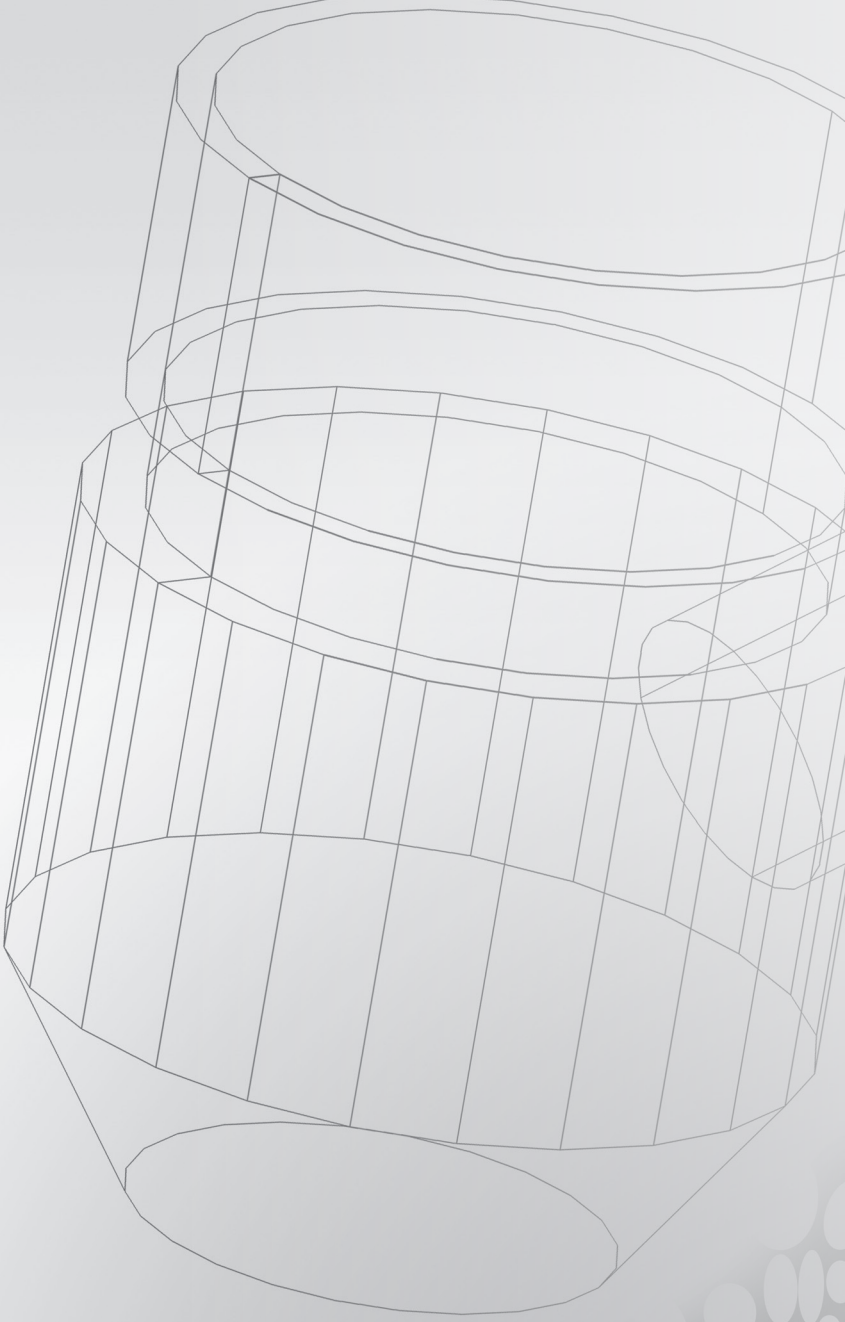
TABLE OF CONTENTS



Chapter 1

General Introduction

Examination of skin lesions for cancer:
Which clinical decision aids and tools are available in general practice?
-review-

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SKIN CANCER

Skin cancer is extremely common; in fact, it has been estimated that one in six persons in the Netherlands will develop skin cancer during their lifetime.[1] The most prevalent forms of skin cancer are basal cell carcinoma (representing 80% of all skin cancers), squamous cell carcinoma (10%), and melanoma (8%). Currently, the incidence of skin cancer is on the rise[2-5], and this increase is due primarily to increased sun exposure. The prognosis for skin cancer depends on the type of tumour and the stage of the disease. Although basal cell carcinomas rarely metastasise, as a result of their growth they can cause serious damage to the surrounding tissue if not treated in time. This risk of local tissue damage also applies to squamous cell carcinomas; in addition, approximately 1-4% of these tumours metastasise. The risk of metastasis depends on the size and location of the tumour. Squamous cell carcinoma has a relative 5-year survival rate of 92-95%.[4] Melanoma has a relative 5-year survival rate of 87%[6], but this rate varies widely depending on the stage of the tumour. For example, patients with stage IV melanoma have a 5-year survival rate of only 15-20%.[7] Therefore, diagnosing and treating skin cancer early is essential for preventing damage to the surrounding tissue and improving survival.

THE PATHWAY OF A POTENTIALLY MALIGNANT SKIN LESION THROUGH THE DUTCH HEALTHCARE SYSTEM

In the Dutch healthcare system, the general practitioner (GP) is the gate-keeper for medical care. This implies that nearly all patients visit their GP first when they discover a skin lesion that they suspect might be malignant. After taking the patient's medical history, the GP then examines the lesion and determines whether it is benign or potentially malignant. Subsequently, the GP has several options for treatment. If the lesion is benign, no action is required, and the patient can be reassured. However, if the lesion is potentially malignant, the GP can either treat the patient or refer the patient to secondary care. If the GP elects to treat the patient, the lesion is usually either biopsied or excised. Although GPs are advised to send all excised lesions to a pathological laboratory for histological examination,[8] this is not always the case.[9, 10] If the GP chooses to refer the patient to a specialist, most of the time the patient is referred to either a dermatologist or a general or plastic surgeon. This specialist then has similar treatment options as the referring GP. He/she can either take no action and reassure the patient or he/she can treat the patient. Depending on the lesion's type and stage, the patient may remain under the care of the GP or specialist.

EXAMINATION OF SKIN LESIONS FOR CANCER: WHICH CLINICAL DECISION AIDS AND TOOLS ARE AVAILABLE IN GENERAL PRACTICE? -REVIEW-

INTRODUCTION

While the incidence of skin cancer is increasing,[2-5, 11-14] campaigns are being used to increase public awareness of this epidemic.[15-21] It can therefore be anticipated that the number of patients consulting a general practitioner (GP) for a potentially malignant lesion of the skin will rise.

It is the task of the GP to diagnose skin malignancies as early as possible while at the same time preventing unnecessary excisions and referrals to secondary care. This is particularly the case in countries where the GP has a gatekeeper role. For the evaluation and management of potentially malignant skin lesions, the GP has several strategies varying from taking medical history and physical examination, teleconsulting a dermatologist, excision or referral. Although several, old, studies have reported on the sensitivity and specificity of specific skin lesions[22-27], to the best of our knowledge, there are no studies on the diagnostic accuracy of GPs for the entire spectrum of potentially malignant skin lesions as presented in general practice. Furthermore studies about late or missed diagnosis of skin malignancies by the GP are lacking. However, it is known that a large percentage GPs feel unsure about their ability to diagnose skin malignancies, rising up to 78% for early melanoma lesions,[25, 28-30] and many skin lesions are either excised by the GP or referred to secondary care.[31, 32] This might not be surprising as dermatology is a specialty in which GPs are hardly trained.[33, 34] It is therefore questionable whether a GP has the skills and tools to diagnose and treat potentially malignant skin lesions. In this study we evaluated whether the GP has sufficient validated clinical decision aids and tools for the examination of potentially malignant skin lesions. We decided to opt for this entire range of skin lesions as we consider this to be the best reflection of daily practice in which, for instance, it might not always be clear at first sight whether a lesion is melanocytic or not.

METHODS

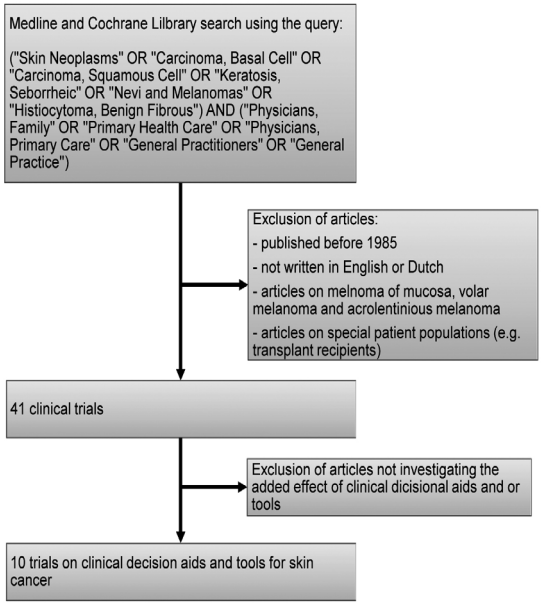
We conducted a review providing an overview of the clinical decision aids and tools available to the GP for the examination of skin lesions for cancer. We therefore looked at the added value in terms of sensitivity and specificity as well as the pros and cons of each option.

Search strategy: A search was conducted in the Medline and Cochrane Library search engines using the following query in Mesh terms: ("Skin Neoplasms" OR "Carcinoma, Basal Cell" OR "Carcinoma, Squamous Cell" OR "Keratosis, Seborrheic" OR "Nevi and Melanomas"

OR "Histiocytoma, Benign Fibrous") AND ("Physicians, Family" OR "Primary Health Care" OR "Physicians, Primary Care" OR "General Practitioners" OR "General Practice"). Exclusion criteria included articles published before 1985, articles written in a language other than English or Dutch, and articles on melanoma of the mucosa, volar melanoma and acrolentiginous melanoma. In addition, articles on special patient populations like transplant recipients were excluded.

This search resulted in 41 clinical trials (October 14th, 2013). However, only 10 were trials on methods and tools for skin cancer. The majority of the other studies investigated the effect of educational, screening or prevention programmes and therefore did not investigate the added effect of clinical decisional aids and or tools. (Fig. I) To enlarge the number of studies, reference lists of the articles were examined as well as articles from personal archives.

Figure I: Flow chart search strategy.



RESULTS

Algorithms for clinical recognition

ABCD(E) criteria

The ABCD criteria were developed in 1985 to help doctors and patients recognise the clinical symptoms of melanoma.[35] ABCD stands for Asymmetry, Border irregularity, Colour variegation and a Diameter > 6 mm. A later amendment suggested adding an E for evolving

(change in size, shape, surface, colour or sensation over time).[36] Although some state that the D-criterion hinders the early detection of melanoma,[37] as melanomas may be smaller than 6 mm,[38-40] a large study of pigmented skin lesions revealed a clear increase in the percentage of melanomas once the limit of 6 mm was exceeded concluding that the guideline of 6 mm is indeed useful.[41]

An advantage of the ABCD criteria is that it makes it easier to distinguish between typical benign naevi and melanomas. However, the distinction between atypical naevi and melanomas remains difficult.[42] In addition, the ABCD criteria are also less suitable for the recognition of nodular melanomas[43, 44] and amelanotic melanomas.[45] If two of the five criteria are present, the ABCDE criteria have a sensitivity of 85.0 - 89.3% and a specificity of 44.5 - 65.3% for melanomas.[42, 46] (Table I)

Glasgow 7-point checklist

The 7-point checklist (and the revised version) are based on seven characteristics which are seen more often in melanomas than in non-melanomas. The checklist was developed in 1985 as a folder for GPs and marked the start of a campaign in Scotland.[47] In the revised version there are three 'major signs': change in size, shape or colour; and four 'minor signs': inflammation, bleeding/crust formation, change in sensation and a diameter ≥ 7 mm. If a lesion has a score of ≥ 3 or if a 'major sign' is present, referral should be considered.[48] One study in primary care showed both the original and revised 7-point checklist performed reasonably well in identifying clinically significant lesions.[49] Furthermore, in a British study conducted on lesions presented at a pigmented lesion clinic, the revised 7-point checklist proved to be more sensitive for diagnosing melanomas than the ABCDE criteria.[50] (Table I)

Other algorithms

Other clinical decision aids for recognition of melanomas include the three Cs, which stand for colour, contour and change.[51] The 'ugly duckling sign'[52], where a naevus that differs from the rest is suspicious for a melanoma, and a combined algorithm that combines the ABCDE and the 7-point checklist are used to approach patients at greater risk of skin malignancies. The latter first tries to identify or rule out a melanoma and then the lesion is classified as typically benign or having basal cell carcinoma or squamous cell carcinoma characteristics.[45] Although one small virtual study found a high sensitivity and specificity for melanoma using the ugly duckling sign[53] (Table I), none of these clinical decision aids have been studied by large randomised trials. However, one Australian trial found that the provision of an algorithm combined with the provision of a camera did not decrease the excision ratio of benign lesions to melanomas.[54]

Additional diagnostic tools

Dermoscopy

Dermoscopy is a non-invasive method in which microstructures of the skin are evaluated using a magnifying apparatus, the dermoscope. The examination starts with an algorithm (step 1) to distinguish melanocytic from non-melanocytic lesions and then, for melanocytic lesions, proceeds with the identification of the melanoma (step 2). Several methods have been developed for the second step.[55-62] In addition, several characteristics and algorithms have been described for the evaluation of non-melanocytic skin lesions. [63-70]

In the hands of dermatologists, dermoscopy increases the diagnostic accuracy,[68, 71-73] reduces the percentage of excisions[74] and leads to a drop in the malignant/benign excision ratio.[75] Only a few studies of dermoscopy in primary care have been conducted. One study evaluating the usefulness of dermoscopy using the '3-point checklist', in the triage of patients with skin tumours, revealed a significant increase in sensitivity (from 54.1% to 79.2%), while the specificity remained the stable at 71.8%. It was striking that also a number of non-pigmented lesions were correctly diagnosed as skin malignancies by the GPs.[76] Another study showed dermoscopy to significantly increase the sensitivity (from 62.7% to 75.9%) for the detection of melanomas while the sensitivity for other pigmented lesions increased slightly but not significantly (53.6% to 57.8%).[77] A third study, demonstrated a sensitivity and specificity of 55% and 89%, respectively, for the diagnosis of pigmented skin malignancies using a dermoscope. The sensitivity and specificity increased to 67.5% and 86.6%, respectively, when the GP could also make a follow-up image after three months. In addition, this study showed that dermoscopy led to a 63% decrease in the prevalence of excision or referral of benign pigmented skin lesions.[78] (Table I)

Although dermoscopy seems favourable, it should be kept in mind that dermoscopy only has added value when used by an expert or at least a trained user.[71] One study even noted a 10% drop in the sensitivity for detecting melanoma when used by untrained dermatologists.[79] Furthermore, it is unclear whether dermoscopy has added value for melanomas smaller than 6 mm.[80-82]

Teledermatology and teledermoscopy

Teledermatology means that a dermatologist, at another location, is consulted for diagnostic and/or therapeutic advice. This can be done with a 'real-time' video consultation, or by 'store-and-forward' photography. In the latter method, the GP prepares overview and detailed photos of the skin lesion that are sent digitally to the teledermatologist, a dermatologist who examines the photos and sends back a recommendation in digital format to the GP.[83]

The reliability of teledermatology has been demonstrated in several studies.[84-93] Advantages of teledermatology are a reduction in the number of referrals up to 51%[84, 85, 94, 95], and educational

value for GPs. [84, 96] Furthermore, the recommendations given via teledermatology are simple to implement [97] and both patients and doctors are satisfied with teledermatology.[84, 96, 98, 99] Disadvantages of teledermatology are an extending of the overall time for consultation.[97, 100] Also dermatologists are less certain of their diagnosis and treatment plan when they have to judge teledermatology.[96] Image and history quality influence the diagnosis agreement,[86, 91, 101-103] however, a randomised controlled trial showed that both image and history quality have no significant influence on treatment agreement.[91] In the Netherlands pigmented lesions are considered less suitable for examination by teledermatology.[104] And, although several studies have shown the utility of teledermatology for pigmented lesions[85, 86, 92, 98, 99, 105, 106], in one study almost 20% of the melanomas would have been mismanaged by teledermatology.[107] Furthermore, the effectiveness and efficiency of teledermatology for suspicious skin lesions have been questioned before as a high proportion of the patients still need a face-to-face consultation.[108, 109]

Additionally, teledermatology can be used to transmit dermoscopic photos, called teledermoscopy. Several studies have shown teledermoscopy to have a high diagnostic accuracy of up to 94%.[110-117] and there is generally good agreement between dermatologists.[118] Furthermore, one study of patients being referred to a hospital skin lesion clinic, showed that up to 74% of these patients could have been managed by their GP without the need of a face-to-face consultation.[112] However, two studies showed teledermoscopy to have a lower diagnostic accuracy compared to face-to-face consultations.[107, 119] And although teledermoscopy had better or equivalent management appropriateness than face-to-face consultations for pigmented lesions, up to 14% of the melanomas would have been mismanaged.[107] Whether the combination of detailed photos with dermoscopic photos further increases diagnostic accuracy is not yet clear.[107, 113, 119] (Table I)

Analysing instruments

Over the last years several, mostly computerised, analysing instruments have been developed to diagnose skin cancer. Examples are SIAscopy, MoleMate, SolarScan, Melafind and spectrophotometry, [120-124] However, only MoleMate™ has been tested in a primary care setting. This system involves a hand-held scanner that sends images directly to a computer. First a dermoscopic image is shown followed by images of the SIAscan (spectrophotometric intracutaneous analysis). These images show epidermal and dermal melanin, vasculature and the collagen within the lesion. Based on an algorithm, a decision can be made about whether the lesion is suspicious and needs further investigation.[125] However, a large randomised controlled trial in primary care revealed that adding this system to best practice did not improve the appropriateness of referral [123], even though it might be cost-effective.[126]

Table I: Sensitivity and specificity of clinical decision aids and tools for the examination of skin lesions for cancer as found in general practice.

Method	Condition	Sensitivity	Specificity	Study
ABCDE method	2 criteria present	85.0-89.3% [42, 46]	44.5-65.3% [42, 46]	Thomas L. et al. 1998 and Benelli C et. al 2003 *
	3 criteria present	65.5–66.6% [42, 46]	79.4-80.0% [42, 46]	Thomas L. et al. 1998 and Benelli C et. al 2003 *
	Unknown	92.7% [50]		Helasmith M.F. et al. 1994 †
7-point checklist	Original version Scoring ≥ 3 points	80.6% [49] (Clinically significant lesions: 62.7%)	61.7% [49] (Clinically significant lesions: 65.0%)	Walter F.M. et al. 2013
	Revised version Scoring ≥ 3 points	91.7% [49] (Clinically significant lesions: 80.9%)	33.1% [49] (Clinically significant lesions: 35.0%)	Walter F.M. et al. 2013
		95.7% [123]	90.6% 123	Walter F.M. et al. 2012 ‡
Ugly Duckling Sign		89% [53]	86% [53]	Scope A. et al. 2008 §
Dermoscopy	3-point-checklist; 2 criteria present	79.2% [76]	71.8% [76]	Argenziano G. et al. 2006
	Training	75.9% [77]		Westerhoff K. et al. 2000 **
	without SDDI	55% [78]	89% 78	Menzies S.W. et al. 2009 ††
	with or without SDDI	67.5% [78]	86.6% 78	Menzies S.W. et al. 2009 ††
Teledermatology	Depending on teledermatologist. Reliability has been demonstrated.			
Teledermoscopy		100% [117]	78% [117]	Moreno-Ramirez D. et al. 2006 ‡‡
		94% [117]		Moreno-Ramirez D. et al. 2006
Molemate		98.5% [123]	84.4% [123]	Walter F.M. et al. 2012 ‡

*Criteria recorded by trained dermatologists. †Lesions presented at a pigmented lesion clinic. ‡Treatment compared to treatment of expert. §Small study on photographs, sensitivity for non-expert dermatologists. Accuracy of referral

**Sensitivity for melanoma, study on photographs. ††For malignant pigmented lesions. Lesions already selected, by naked eye examination, for biopsy or referral. ‡‡Regarding the decision to refer the patient or not.

DISCUSSION

Summary of evidence

In this review we have summarised the clinical decision aids and tools available to the GP for the examination of potentially malignant skin lesions. We have found that there is a lack of sufficiently validated clinical decision aids and tools for the examination of these lesions. Only the 7-point checklist has been studied in primary care. However it was not compared to care as usual and the additional value of this checklist remains unclear. In addition, controlled clinical trials of the available tools in primary care are scarce.

A validated diagnostic tool for the examination of all non-melanocytic suspicious skin lesions is not available. However, dermoscopic characteristics have been described to recognise these lesions.[63-66, 69] A sound validation for dermoscopy applied to all suspicious skin lesions is still lacking, but there are indications that dermoscopy conducted by GPs might lead to an improved assessment.[76]

For the clinical, non-dermoscopic, examination of pigmented suspicious skin lesions two major diagnostic clinical decision aids have been developed, both to diagnose or exclude melanomas. The ABCDE criteria offer a handy guideline for physical examinations due to their ease of application and sensitivity and specificity of 85.0-89.3% and 44.5-65.3%, respectively.[42, 46] The GP must realise, however, that these criteria can be deceptive for small, i.e. < 6 mm, amelanotic and nodular melanomas. Research has shown that nodular melanomas make up 10% of all melanomas.[127] Also the E-criterion must be treated with care as 5.3% of normal naevi grow in a year[128] and in patients younger than 50 years only 3% of the changed naevi are melanomas.[129] The 7-point checklist is somewhat more difficult to remember. It has a sensitivity of 79-100% but a low specificity of 35.0-65.0%.[49, 50, 130] Because of this low specificity, the 7-point checklist seems less suitable in the GPs practice where benign skin lesions are much more common than malignant skin lesions. On the other hand, at least in secondary care, the 7-point checklist has a higher sensitivity which is of course very important as no melanoma should be missed. However, one might question whether these clinical decision aids can be used in primary care. For instance, laypersons did not seem to be able to use the A B and C criteria reliably to differentiate benign from malignant lesions[131] and we do not know if GPs can. Furthermore, it has been stated that a large part of clinical expertise might be experience based next to analytical pattern recognition[132], so perhaps clinical decision aids will not be the solution for a high diagnostic accuracy? Unfortunately the ABCD(E) criteria have only been studied in secondary care and also for the 7-point checklist no comparison to care as usual is available.

Another option for the examination of melanocytic suspicious skin lesions is to use an additional diagnostic tool like the dermoscope. Three studies found an increase in the sensitivity when it was used by GPs.[76-78] Criticisms of these studies are that they did not examine the long-term effects of the training and it might be possible that the participating GPs were specifically interested in dermatology (selection bias). The first comment also applies to many studies of dermoscopy conducted by a dermatologist. It is clear that a thorough training must precede the use of the dermoscope; it is less clear whether the effect of this training disappears over time and whether a minimal number of abnormalities per unit of time must be examined with the dermoscope to maintain the positive effect. New, computer-assisted, analysing instruments like the MoleMate™ system have not yet proven their value in primary care.

If the GP is not able to come to a diagnosis, or if there are questions about policy, teledermatology might be used. There is an on-going discussion, at least in the Netherlands, as to whether teledermatology is suitable for the triage of pigmented lesions. There are several studies in which teledermatology proved useful for pigmented lesions [85, 92, 98, 99, 105, 106], although one study showed that almost 20% of the melanomas would have been mismanaged by teledermatology.[107] In 6 out of 7 of these melanomas the confidence level of the teledermatologists was moderate to high. However, the insurance that all included lesions were already referred to secondary care and selected for biopsy, could have biased the confidence level of the teledermatologists. It is to be expected that when a lesion is forwarded by a GP to a dermatologist through teledermatology, the assessment will have a lower confidence level and thus will sooner include the advice to refer or biopsy the lesion. Although teledermoscopy might improve diagnostic accuracy, a large controlled trial is needed to evaluate the effect of adding a dermoscopic photo to a detailed photo for all potentially malignant skin lesions.

Limitations

As clinical trials on suspected skin lesions conducted in primary care are scarce, small studies and studies only conducted only in secondary care were included as well. This means that there was a large difference in the quality of the included studies. Also, this might have led to spectrum bias as studies from different clinical settings, e.g. primary care, secondary care and specialised skin clinics, were included. Furthermore, it is important to realise that in studies of skin lesions, the sensitivity and specificity of the clinical decision aid or tool can never be assessed precisely because it is unethical to excise all lesions for histopathological diagnosis (gold standard). And, although a prolonged follow up might partly overcome this problem by finding initially missed malignancies, this is unfortunately not usually part of the study design.

Conclusions

With this review we conclude that there is a lack of validated clinical decision aids and tools for the examination of potentially malignant skin lesions in primary care. None of the available clinical decision aids have been compared to care as usual, and the number of controlled clinical trials in primary care for the available tools are scarce as well. Nevertheless, the following recommendations can be drawn from this review:

- Clinical trials in primary care are needed to determine the value of 1) clinical decision aids for clinical recognition in primary care, 2) dermoscopy of all potentially malignant skin lesions by GPs after formal training, 3) teledermatology by GPs of suspected pigmented skin lesions, and 4) the addition of teledermoscopy to teledermatology.
- At this point in time, there seems to be no clear evidence to exclude pigmented lesions from teledermatology. Nevertheless, GPs and teledermatologists should be aware of the possible limitations of teledermatology of pigmented lesions.

RATIONALE AND AIM OF THIS THESIS

Given the high incidence of skin cancer and the importance of early diagnosis as discussed above, it is surprising that GPs are not better trained to diagnose skin cancer, and it is equally surprising that there is a lack of sufficiently validated clinical decision aids and tools for evaluating potentially malignant skin lesions in general practice. In addition, many GPs are insecure with respect to their ability to diagnose skin lesions.

The ultimate goal of this thesis is to create an impetus for an improved and more evidence-based approach for diagnosing potentially malignant skin lesions in general practice. To achieve this goal, the first aim of this thesis was to identify the current state of potentially malignant skin lesions in general practice. How often are potentially malignant skin lesions encountered in the GP's office, and what happens with these patients? The second aim of this thesis was to investigate the value of a diagnostic tool – the dermoscope – for the evaluation of potentially malignant skin lesions in general practice.

OUTLINE OF THIS THESIS

The burden that potentially malignant skin lesions placed on general practitioners during the past decade is described in *Chapter 2*. This chapter also addresses the use of the various treatment options available to the GP for treating potentially malignant skin lesions. The use of a histological examination of skin lesions by both primary and secondary caregivers, and the possible influence of a financial incentive, is described in *Chapter 3*. *Chapter 4* compares the diagnostic accuracy of using a dermoscope with the accuracy achieved with care as usual. It

also describes the cost-effectiveness of performing dermoscopy in general practice. *Chapter 5* provides insight into the clinically relevant aspects of dermoscopy compared to care by describing the diagnostic accuracy for (pre)malignant skin lesions. *Chapter 5* also addresses the malignancies that were handled using a watchful waiting approach (false negatives) and the treatment of benign lesions. Finally, *Chapter 6* summarises and discusses the results of all chapters. Furthermore, it discusses the implications of our results for education, clinical practice and future research.

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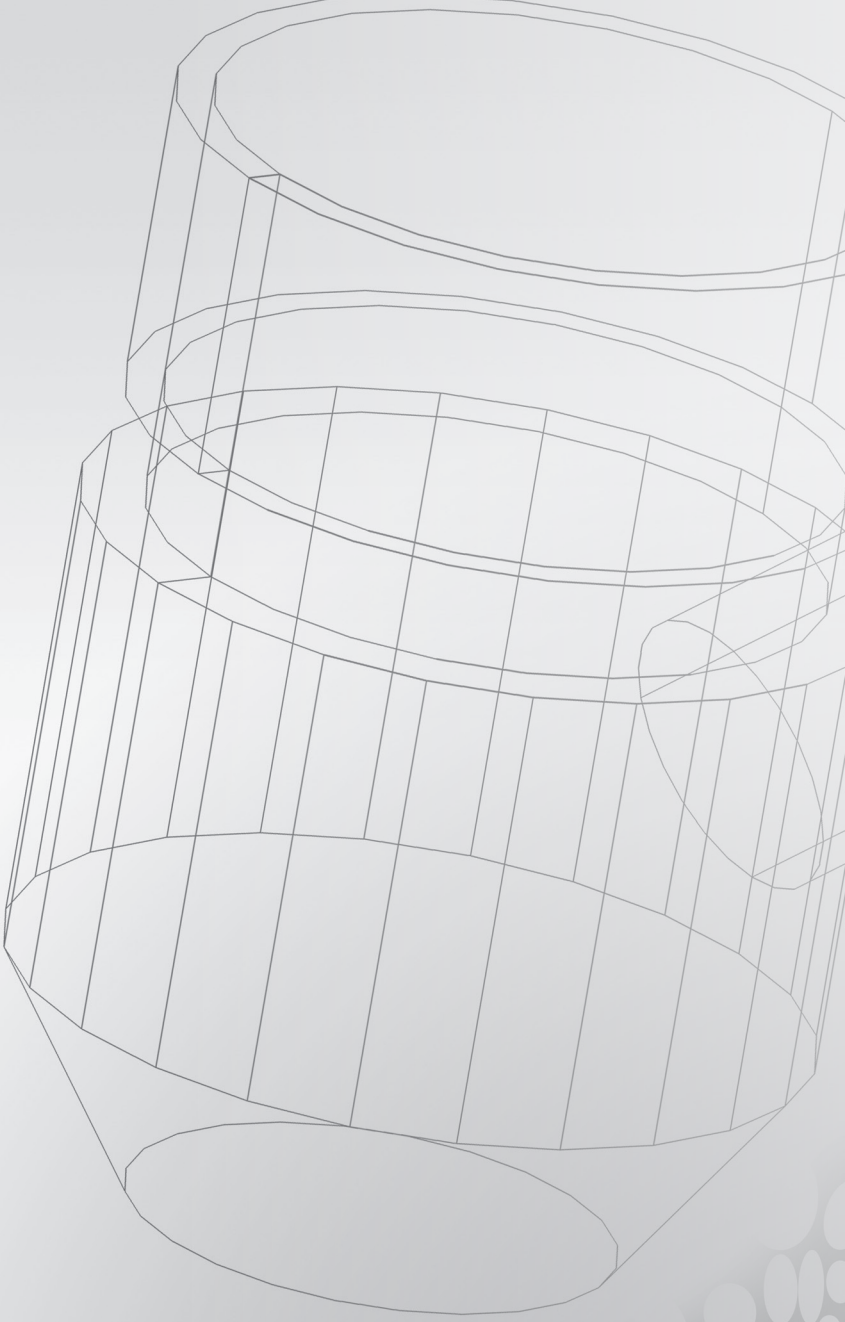

Chapter 2

Potentially malignant skin lesions: an increasing burden on general practice

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Submitted

ABSTRACT

Background Skin cancer is believed to impose a heavy burden on healthcare services, but the burden of potentially malignant skin lesions on primary healthcare has never been evaluated. Therefore the aim of this study was to determine the demand for care in general practice due to potentially malignant skin lesions.

Methods Registry study based on data (2001-2010) from the Registration Network Groningen. This is a general practice registration network in the northern part of the Netherlands with an average annual population of approximately 30,000 patients. All patient contacts are coded according to the International Classification of Primary Care (ICPC). Consultations for potentially malignant skin lesions were selected according to the assigned ICPC codes. Subsequently, the number of consultations per year and the annual percent change in number of contacts (using the JoinPoint regression program) were calculated and analysed. Additionally, the percentage of patients referred to secondary care or receiving minor surgery within one year after the first contact were calculated.

Results From 2001 onwards we found an annual increase in demand for care due to potentially malignant skin lesions of 6.8% ($p<0.01$) and in 2010 the benign:malignant ratio was 14:1. In total 14.3% of the patients were referred and after 2006, minor surgery was performed on 29.5% of the patients. Most surgeries and referrals took place within 30 days.

Conclusions Potentially malignant skin lesions impose an increasing burden on primary healthcare and most likely on healthcare costs as well. General practitioners should therefore be trained in diagnosing potentially malignant skin lesions, as a high diagnostic accuracy can save lives in the case of melanoma, and may also prevent unnecessary, costly, excisions and referrals to secondary healthcare.

BACKGROUND

Skin cancer incidence is rising.[1-6] In the Netherlands, one in six people are expected to develop skin cancer.[7] Public awareness is also rising as a result of many public information campaigns[8-11] and this may lead to an increased consultation rate. These consultations also include non-malignant skin lesions. In fact, the majority of patients visiting their physician for a potentially malignant skin lesion do not have skin cancer. De Vries has suggested that for every new case of skin cancer another 20-50 patients will consult their general practitioner (GP) or dermatologist.[12] This estimate lacks solid evidence, but seems to be in line with daily practice.

In the Netherlands, the GP has a gatekeeper role and patients visit their GP first for any health-related question. The GP can perform a diagnostic procedure, which may include an excision or referral to the dermatologist in the case of suspected lesions. Despite the large number of encounters for skin lesions, many GPs lack a solid training in dermatology.[13, 14] In contrast to the UK[14], no specific guideline for skin lesions suspected of malignancy is available in the Netherlands.

We believe that knowledge on healthcare demands for potentially malignant skin lesions is important. It may identify areas for training as well as revealing possibilities for substitution of care. Therefore, the aim of this study was to determine the demand for care in general practice due to potentially malignant skin lesions for the period 2001-2010. We were particularly interested in the consultation rates and subsequent treatments by GPs, including watchful waiting, excision of the lesion and referral to secondary care.

METHODS

We performed a retrospective analysis on data from the Registration Network Groningen (RNG). This network was established in 1989 and consists of patient registrations of three general practices with 17 GPs in the north-eastern part of the Netherlands. The RNG includes a dynamic population with an average annual population of approximately 30,000 patients. For all patients, both symptoms and diagnoses are coded (by the GPs), according to the International Classification of Primary Care (ICPC). [15, 16] Treatments such as minor surgery and referrals are registered as well. All GPs in this network are especially trained for this type of ICPC registration.

All patients aged 18 years and older were selected, with a consultation for potentially malignant skin lesions between 2001 and 2010. To identify consultations for potentially malignant skin lesion without running the risk of also selecting too many consultations for other reasons, 2 GPs (KvdM and WvdH; both > 25 years experience) and 1 researcher (CK) selected the ICPC codes. Consequently, the following ICPC codes S04 (Lump/swelling localised), S26 (Fear of

cancer of skin), S77 (Malignant neoplasm of skin), S79 (Benign neoplasm of skin, other), S80 (Unspecified neoplasm of skin, other), S81 (Haemangioma/lymphangioma), S82 (Naevus/mole), S83 (Congenital skin anomaly, other) and S99 (Skin disease, other) were used for this analysis. The latter ICPC code was included because it also includes actinic keratosis. (See appendix)

We calculated the annual number of contacts, referrals and minor surgery for potentially malignant lesions per 1,000 patients. For this, we first calculated the total number of patients per year in the database. As the RNG consists of a dynamic population, this was done by counting the true number of person-years for each year based on the actual days during the year in which the patient was present in the database (i.e. registered at one of the practices).

Subsequently, we assessed which percentage of the patients received an intervention, i.e. either minor surgery performed by their GP or referral to secondary care, within 1 year after their first consultation for one of the above mentioned ICPC codes. Due to the small number of annual consultations (<25), codes S26, S81 and S83 were not included in the analysis. For minor surgery, we selected patients with a first visit from 2006 onwards. This period was chosen, because from that year onwards a new financial contract for GPs was introduced which led to improved registration of minor surgery. Before 2006 no trustworthy data on minor surgery could be retrieved. However, referrals have always been registered and for this intervention we selected the period from 2001 onwards. A first visit was defined as having no earlier contact for the analysed ICPC code in the database.

Analyses

Slope differences from zero at alpha 0.05 and the annual percent change (APC) in number of contacts, referrals and minor surgery were estimated and analysed for trend significance, using the JoinPoint Regression Program, version 3.5.2. October 2011 of the Statistical Research and Applications branch of the US National Cancer Institute. This was done for all lesions as well as separately for malignant and benign lesions.

Descriptive analyses were used to report the percentage of patients being subjected to an intervention, the median time to the intervention and the percentage of patients with an intervention 30 and 90 days after the first consultation. For this, SPSS version 18 was used.

A difference with a p-value <0.05 was considered significant.

As all data were received anonymously no ethical approval for this study was needed. This was confirmed by the Medical Ethical Board of the University Medical Center Groningen

RESULTS

On average, there were 22,343 patients aged 18 years and older per year in this study.

Number of contacts per year:

From 2001 to 2010, 22,390 contacts of 9,119 different patients (median number of contacts: 2) for potentially malignant skin lesions were registered. The total number of contacts per year increased by 51.9% from 82.8 contacts / 1,000 patients in 2001 to 125.8 contacts / 1,000 patients in 2010. This was a significant increase with an annual percent increase of 6.8 ($p < 0.01$). (Table 1, Fig. 1) This increase was shown for both malignant (ICPC S77; annual percent change 11.8) and non-malignant (other ICPC codes; annual percent change 6.5) lesions (Fig. 2). In 2010 only 1 in 14 potentially malignant skin lesions was malignant. (Table 1)

Table 1: Number of contacts per year / 1,000 patients (raw number of consultations in the database).

Year	S04 (Lump/swelling localised)	S77 (Malignant neoplasm of skin)	S79 (Benign neoplasm of skin, other)	S80 (Unspecified neoplasm of skin, other)	S82 (Naevus/mole)	S99 (Skin disease, other)	S26; S81; S83 (Fear of cancer of skin, Haemangioma/ lymphangioma and Congenital skin anomaly, other)	Total
2001	22.2 (493)	3.3 (73)	20.9 (465)	3.6 (81)	22.9 (510)	8.7 (194)	1.1 (25)	82.8
2002	23.0 (505)	4.0 (88)	19.4 (427)	2.5 (55)	19.3 (425)	5.0 (110)	1.1 (24)	74.3
2003	21.9 (485)	4.8 (107)	19.8 (438)	1.7 (38)	22.1 (488)	9.5 (211)	1.4 (31)	81.3
2004	22.1 (496)	3.6 (81)	20.5 (461)	1.9 (42)	20.1 (452)	11.1 (249)	0.7 (15)	80.0
2005	23.4 (536)	6.7 (153)	22.7 (520)	0.9 (21)	19.9 (456)	13.4 (307)	0.7 (17)	87.8
2006	31.2 (685)	9.1 (199)	26.1 (574)	2.2 (48)	20.6 (452)	14.2 (311)	1.4 (31)	104.7
2007	30.0 (668)	10.4 (232)	24.5 (547)	4.0 (89)	28.1 (626)	16.7 (372)	1.2 (27)	114.9
2008	29.8 (670)	7.2 (161)	29.7 (667)	4.8 (109)	30.5 (685)	16.5 (372)	1.6 (36)	120.0
2009	35.3 (795)	7.6 (172)	26.2 (592)	5.4 (121)	33.0 (745)	20.8 (470)	1.2 (27)	129.6
2010	32.0 (720)	8.4 (189)	27.6 (621)	5.2 (116)	29.2 (657)	22.4 (504)	0.9 (21)	125.8

Figure 1: Total number of contacts per 1,000 patients per year. (line = trend line, APC = annual percent change)

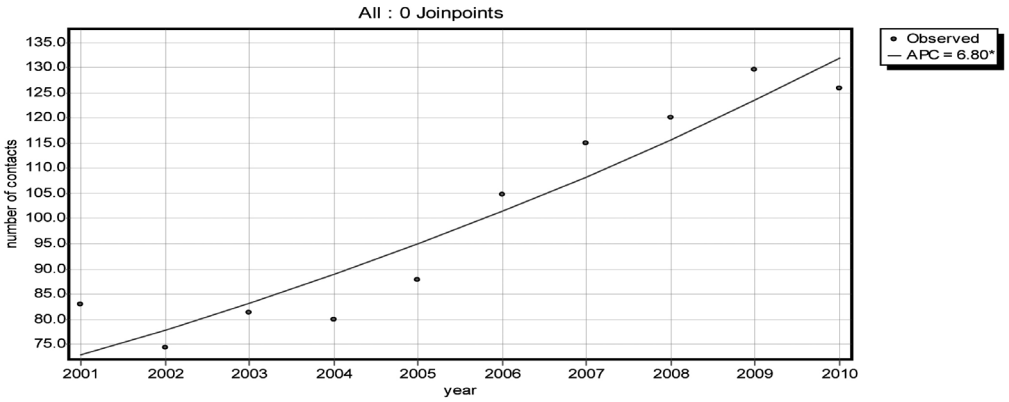
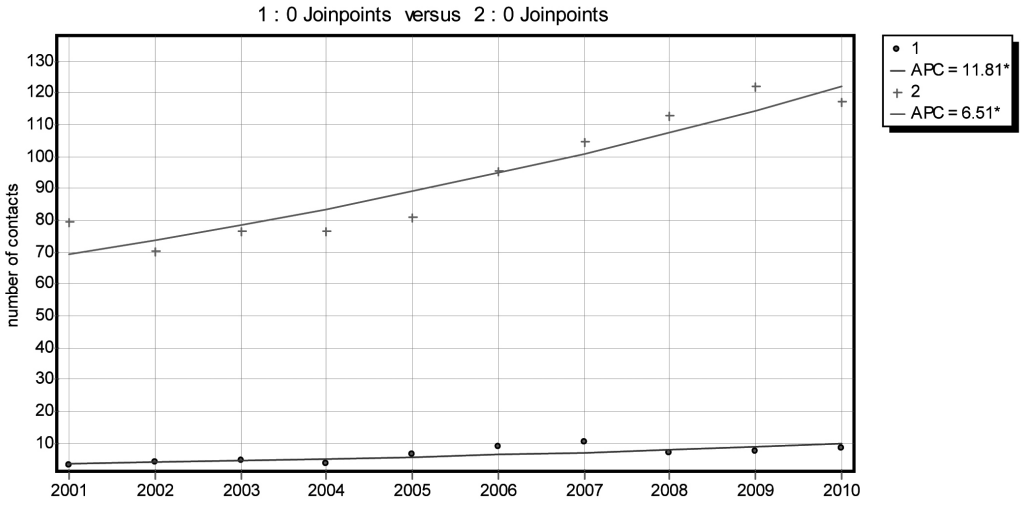


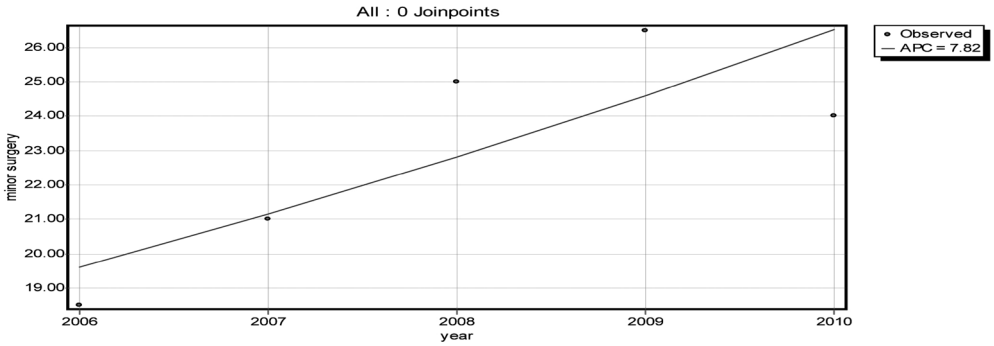
Figure 2: Total number of contacts for malignant (•) and benign (+) skin lesions per 1,000 patients per year. (line = trend line, APC = annual percent change)



Patients receiving minor surgery:

A total of 6,246 patients had a first visit for a potentially malignant skin lesion from 2006 onwards. In 29.5% of these patients, GPs performed minor surgery within one year after their first contact. The median time from the first contact to minor surgery was 6 days. After 30 days, 91.9% of all minor surgery had taken place, after 90 days this percentage increased up to 96.9%. The total number of patients receiving minor surgery increased from 18.5 / 1,000 patients in 2006 to 24 / 1,000 patients in 2010, which was an annual percent increase of 7.8 ($p = 0.09$). (Fig. 3)

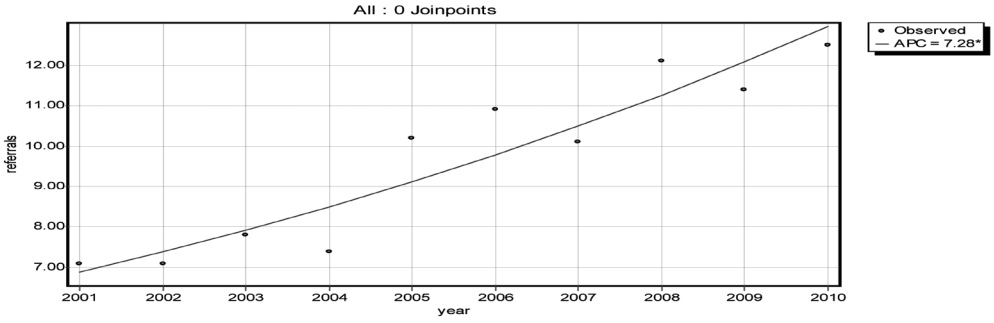
Figure 3: Minor surgery (number of excisions) per 1,000 patients per year (line = trend line, APC = annual percent change)



Patients referred to secondary care:

Of the 11,449 patients with a first contact for a potentially malignant skin lesion from 2001 onwards, 14.3% were referred to secondary healthcare at or within one year after the first consultation. As more than half of the patients were referred on the day of the consultation, the median time to referral was 0 days; 87.7% of the patients were referred within 30 days after the first visit and after 90 days, more than 92% of the referrals had taken place. The total number of referrals increased from 7.1 / 1,000 patients in 2001 up to 12.5 / 1,000 patients in 2010. This corresponded with a significant annual percent increase of 7.3 ($p<0.01$). (Fig. 4)

Figure 4: Total number of referrals per 1,000 patients per year (line = trend line, APC = annual percent change)



DISCUSSION

Summary of main findings

This study shows that potentially malignant skin lesions impose an increasing burden on general practice. During the period 2001-2010, the demand on care for potentially malignant skin lesions increased significantly ($p<0.01$) with an annual percent increase of 6.8, leading to 125 contacts / 1,000 patients / year. The majority of these contacts are due to benign lesions. A large proportion, 14.3%, of the new lesions are referred to secondary care and the GP performed minor surgery on almost 30% of the new lesions. Almost all referrals and minor surgery took place within 30 days after the first visit, suggesting that GPs make prompt decisions concerning the treatment.

Context with other literature

In this study we found that an average Dutch GP practice, with 2,350 patients, was consulted 357 times for potentially malignant skin lesions in 2010. Based on 255 annual working days, this entails 1.4 GP consultations each day. This increasing demand approaches the estimated increase reported by de Vries et al. of up to 2 consultations / day in the year 2015.[12] It is common knowledge that dermatology is a specialist area GPs often refer to.[17] This study shows that potentially malignant skin lesions must constitute a large group of these referrals. Within 1 year after the first visit, 14.3% of the patients were referred to secondary care. An even greater proportion of the patients, i.e. 29.5%, had their skin lesion removed by the GP. These percentages are comparable to the 10.2% and 27.4% respectively observed by van Dijk et al.[18] The minor differences observed are probably due to a different selection of skin lesions as van Dijk et al. only studied benign neoplasms of the skin and naevi, and included episodes of care instead of first contacts.

Implications of results

As demonstrated by our study, GPs are frequently and increasingly confronted with the care of potentially malignant skin lesions. Most of these lesions are benign and although the number of contacts for malignant lesions are increasing at a higher rate than the number of contacts for benign lesions, in 2010, only 1 in 14 potentially malignant skin lesions was malignant. Furthermore, the total number of excisions (registered as minor surgery) and referrals showed an annual increase of 7.8% and 7.3% respectively, which is slightly higher than the 6.8% increase in the total number of contacts for potentially malignant skin lesions found in this study. This increasing demand for care in general practice, but as seen by the increase in referrals to secondary care as well, is likely to result in an increasing burden on healthcare costs. It is, therefore, important that GPs are adequately trained to diagnose and treat potentially malignant skin lesions as early detection can save lives, in the case of melanoma, while ruling

out malignancy at an early stage may prevent unnecessary, costly, excisions and referrals to secondary care. Yet GPs in both the UK and the Netherlands receive only limited training in dermatology[13, 14] and it has been suggested that GPs' skills of diagnosing skin lesions could be improved.[19] Ensuring that GPs and GP registrars acquire a satisfactory level of dermatological knowledge for the accurate diagnosis and treatment of skin cancer should therefore be a priority.

Strenghts and limitations

As in every healthcare database, the reliability is dependent on the accuracy of registration. Therefore all GPs participating in the RNG receive special training to maintain optimal registration. A limitation of this database is that it does not distinguish between consultations that are genuinely for a potentially malignant skin lesion and those that are not. We believe that, based on the selected ICPC codes, we identified most of the suspected lesions without selecting too many non-suspected lesions. Nevertheless the numbers should be interpreted with caution. Also, in this database it is not clear whether the reason for the next consultation was prompted by exactly the same lesion or another lesion. As this may bias the percentage of patients subjected to minor surgery or who were referred to secondary care, we decided to consider only the data of the first visit and the following year for the analysis. However, we are confident that the analysis based on this large primary care database enabled us to draw valid conclusions on the burden that potentially malignant skin lesions impose on general practice. And although this study was conducted in the northern part of the Netherlands, we believe that with increasing incidence rates of skin cancer all over Europe[3-5], the observed trends in this study should be similar in other countries.

Conclusions

Potentially malignant skin lesions impose an increasing burden on primary healthcare and most likely on healthcare costs as well. Especially, as many of these lesions are either excised or referred to secondary healthcare. General practitioners should therefore be trained in diagnosing potentially malignant skin lesions, as a high diagnostic accuracy can save lives in the case of melanoma. Additionally, it may also prevent unnecessary, costly, excisions and referrals to secondary healthcare.

Acknowledgements:
We would like to thank Marco Blanker for his valuable comments on this paper.

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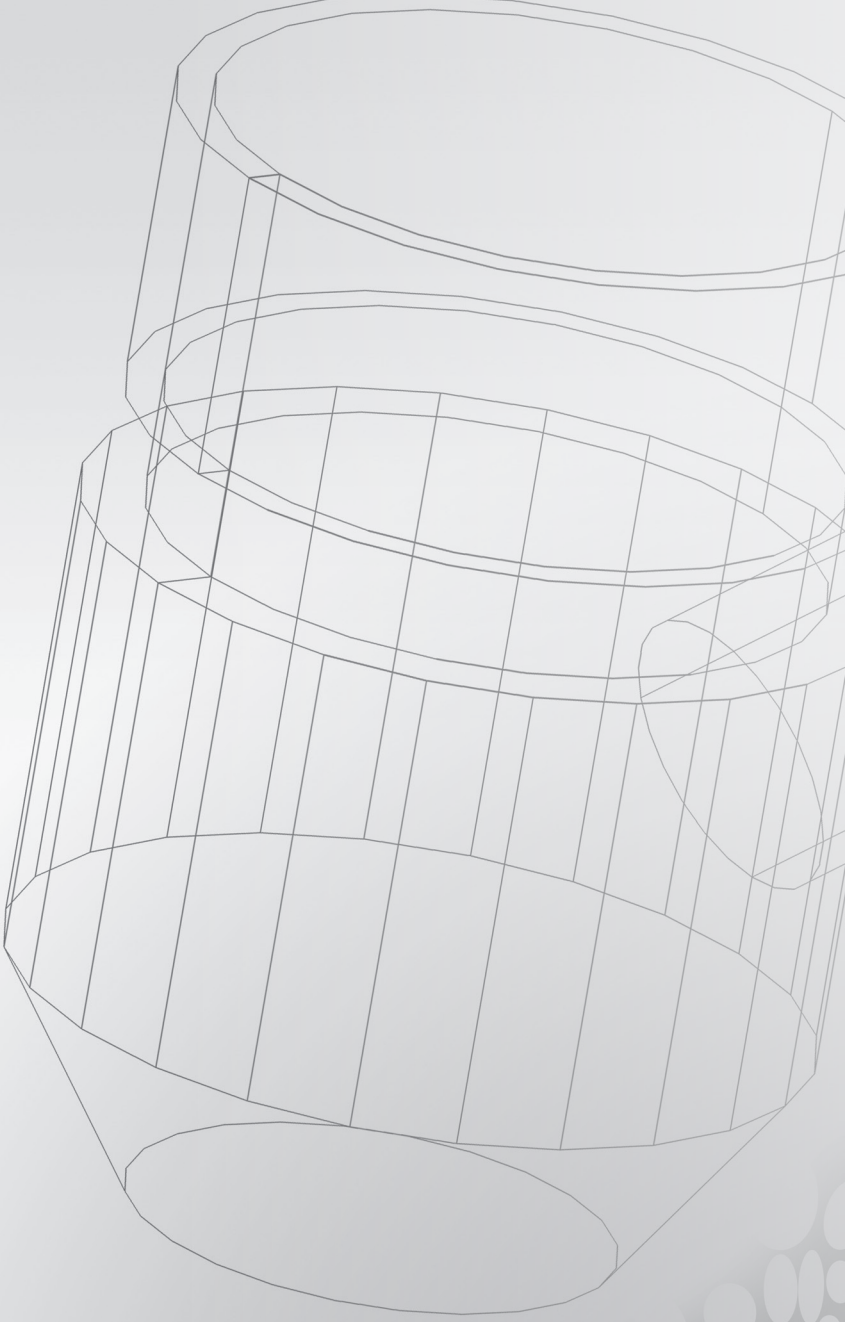
ADDENDUM

ICPC codes

Code	Description
S04	Lump/swelling localised
S26	Fear of cancer of skin
S77	Malignant neoplasm of skin
S79	Benign neoplasm of skin, other
S80	Unspecified neoplasm of skin, other
S81	Haemangioma/lymphangioma
S82	Naevus/mole
S83	Congenital skin anomaly, other
S99	Skin disease, other

http://www.rivm.nl/who-fic/cdromthesaurus/Pagerenglish.pdf



Chapter 3

Financial incentive stimulates histological submission of skin tissue samples by Dutch general practitioners

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Submitted

ABSTRACT

Background A new financial contract for Dutch general practitioners (GP) was introduced in 2006. One of its main goals was substitution from secondary care to primary care.

Aim To determine the effect of introducing a new financial contract for primary care on the number of histological submissions of skin tissue samples by GPs and hospital specialists.

Design and setting Retrospective study using an anonymised database at a histological laboratory of a large regional hospital in the Netherlands.

Methods Selection of skin tissue sample submissions by GPs and hospital specialists from 2001 to 2010. Subsequently, analyses of the number, trend and change in trend of these submissions.

Results More than 84,000 skin tissue samples were submitted for analysis to the pathology laboratory. GPs accounted for 45.9% of these submissions. The number of skin tissue sample submissions gradually increased over the study period for both GPs and hospital specialists. However, only the number of skin tissue sample submissions by GPs showed a significant upward inflexion after 2006. The proportion of benign lesions remained stable.

Conclusions Skin tissue sample submissions for histological analyses have steadily increased between 2001 and 2010. The introduction of a new financial contract probably stimulated the number of skin tissue sample submissions by GPs without a widening of range of indication for excision, but appears to have had no effect on the number of skin tissue sample submissions by hospital specialists. We could therefore not demonstrate that a financial incentive has resulted in substitution from secondary to primary care.

INTRODUCTION

In the Netherlands, the general practitioner (GP) has a gatekeeper role. This means that all patients first have to visit their GP, who can then decide to treat the patient themselves or to refer the patient to secondary care. In 2006 a new financial contract for Dutch GPs came into effect. This stipulated that GPs would be paid for the medical care they actually delivered, e.g. getting paid for each excision / biopsy of a skin lesion, instead of being paid by a lump sum. One of this contract's main goals was to stimulate the substitution of secondary care to primary care.[1]This substitution effect might be reflected in a reduced number of referrals to secondary care, but also in a shift in the number of biopsies and excisions of skin lesions performed from secondary care to primary care. The risk of a financial incentive is that it leads to a widening of the range of indication for excision, such as also including evident benign lesions. A similar financial contract was introduced in the United Kingdom (UK) in the early 1990s. This led to an increase in the number of excisions, up to 41% [2], and an even greater increase in the number of skin tissues samples submitted for analysis to the pathology laboratory.[3-7] Furthermore, no clear compensatory decrease in the number of hospital referrals was seen.[2] However, these studies only investigated short-term influence and no recent data on pathological submissions by GPs, in either the UK or the Netherlands, have been published. In this study, we investigated whether a change in the number of skin tissue samples submitted for histological analyses by Dutch GPs and hospital specialists has occurred since the introduction of the new financial contract for GPs in 2006. In addition, we looked at the proportion of benign and malignant lesions submitted. We did this by analysing the skin tissue sample submissions to a pathology laboratory between 2001 and 2010.

METHODS

Data

We used retrospective data of skin tissue samples submitted to the pathology laboratory of a large regional hospital (Martini Hospital, Groningen). This laboratory serves the northern region of the Netherlands and is part of the nationwide network and registry of histology and cytopathology in the Netherlands (PALGA). Approximately 80% of the GPs in this region and all specialists at the Martini hospital send their skin tissue samples to this laboratory for histological analysis. The database incorporates identifiers for the year of submission, the patient (e.g. age and gender), the specialist and the diagnosis. The pathologist who assessed the submitted sample classified the diagnosis. This classification is structured along five axes: topography, morphology, function, procedure and diseases.[8] Data on samples of skin excisions and biopsies performed between 2001 and 2010 were used for this study.

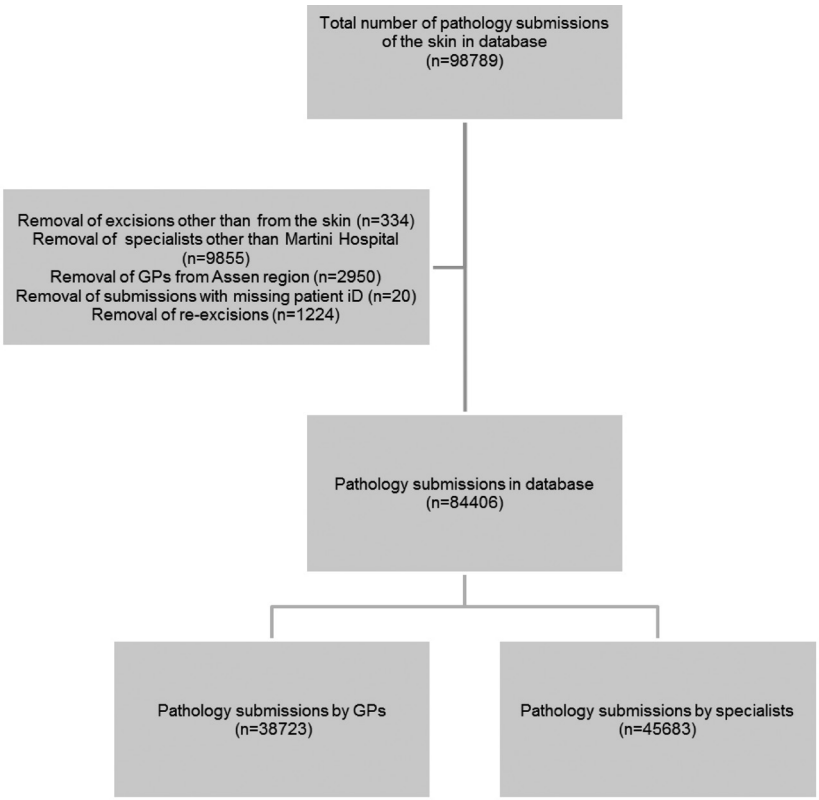
No written informed consent was given by patients for their information to be stored in this

registry. However, the Medical Ethical Board of the University Medical Center Groningen specifically waived approval for this study as all data were received and analysed anonymously and written informed consent was not required.

Inclusion

All skin tissue samples, biopsies and excisions, submitted to the Martini Hospital pathology laboratory were identified and selected. Malignancies were selected by identifying all data which contained the codes for melanoma, squamous cell carcinoma and basal cell carcinoma. Premalignancies were likewise selected using the codes for melanoma in situ / lentigo maligna, squamous cell carcinoma in situ / Bowen's disease or actinic keratosis.

Figure 1: In- and exclusion of skin tissue samples.



Exclusion

The classification used in the database also includes special codes for re-excisions. In our analyses all re-excisions were excluded. As we wanted to analyse the number of skin tissue sample submissions in the region, it was important that the region, and the number of inhabitants, remained stable over the period studied. Therefore all samples submitted from the town Assen (hospital specialists and GPs) and the surrounding region were excluded, as this region only started to use the laboratory's service in 2007 after the implementation of the contract. We also excluded skin samples with a missing patient ID and samples which were coded as being from the skin but were in fact derived from another part of the body, e.g. only subcutis. (Fig. 1)

Statistical analyses

Database and patient characteristics were analysed using descriptive statistics.

Linear by linear association chi-square test statistics were used to explore differences in trends in the number of skin tissue sample submissions between GPs and hospital specialists. All analyses were performed using SPSS version 18.

In addition, temporal trends in the number of skin tissue sample submissions were analysed using the JoinPoint Regression Program, version 3.5.2. (October 2011) of the Statistical Research and Applications branch of the US National Cancer Institute. Based on permutation analyses[9], joinpoints of statistical inflexions in trends were identified for the number of skin tissue submissions of both GPs and hospital specialists.

RESULTS

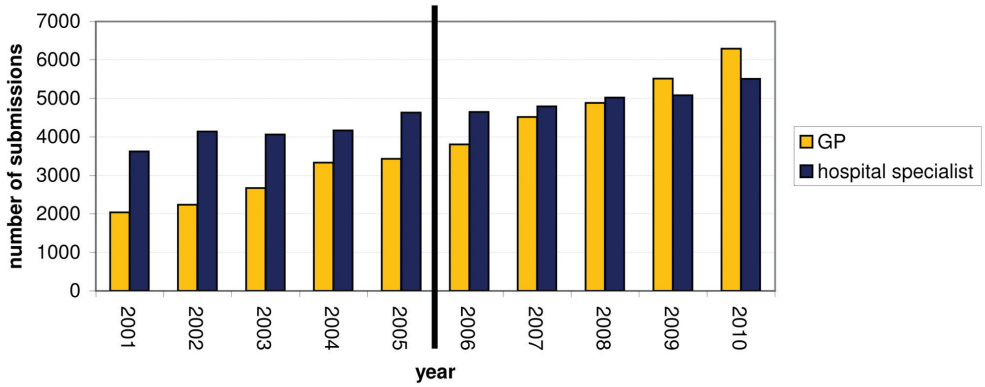
Number of pathological submissions: A total of 84,406 skin tissue samples were submitted for analysis to the pathology laboratory. Database and patient characteristics are shown in Table 1.

Table 1: Characteristics of pathological skin tissue sample submissions by GPs and specialists. Values are absolute numbers unless stated otherwise.

	GP submissions	Specialist submissions
Database characteristics		
Submitting GPs / specialists	279	128
Submissions (%)	38,723 (45.9)	45,683 (54.1)
Patient characteristics		
Percentage female	61.6	55.2
Average age ± standard deviation (years)	47.8 ± 19.2	57.0 ± 20.7
Malignancies (%)	2,901 (7.5)	13,745 (30.1)
Premalignancies (%)	1,739 (4.5)	3,366 (7.4)

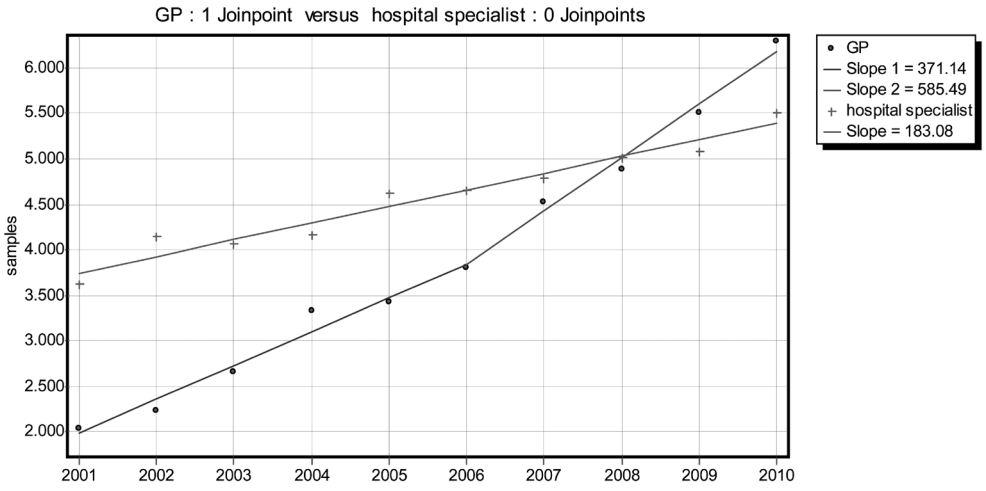
Both the GPs and hospital specialists showed an increase in the number of skin tissue sample submissions over the years, with the increase being more pronounced for GPs than for hospital specialists ($p < 0.001$). From 2009 onwards, GPs submitted more skin tissue samples to the laboratory than the hospital specialists. (Fig. 2)

Figure 2: Number of skin tissue sample submissions per year for GPs and hospital specialists. (bold vertical line = introduction of 2006 contract)



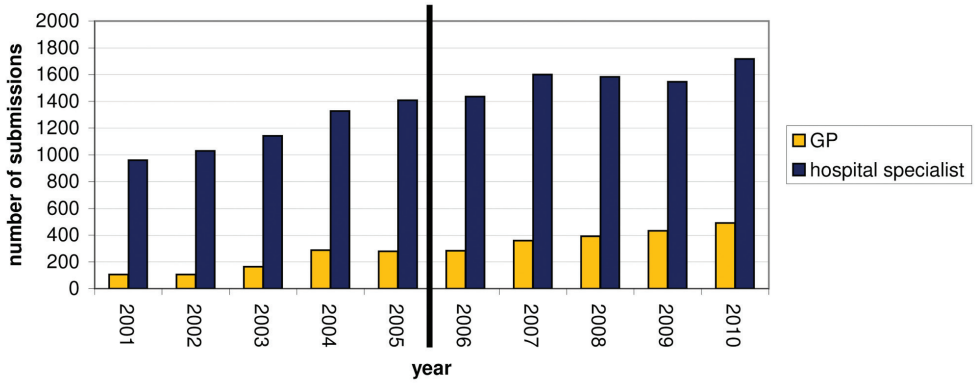
The number of skin tissue sample submissions by GPs demonstrated a significant upward inflexion in trend between 2006 and 2007 ($p = 0.049$). We observed no change in trend in the number of skin tissue samples submitted by hospital specialists between 2001 and 2010 ($p = 0.96$). (Fig. 3)

Figure 3: Joinpoint regression of number of skin tissue sample submissions by GPs and hospital specialists.



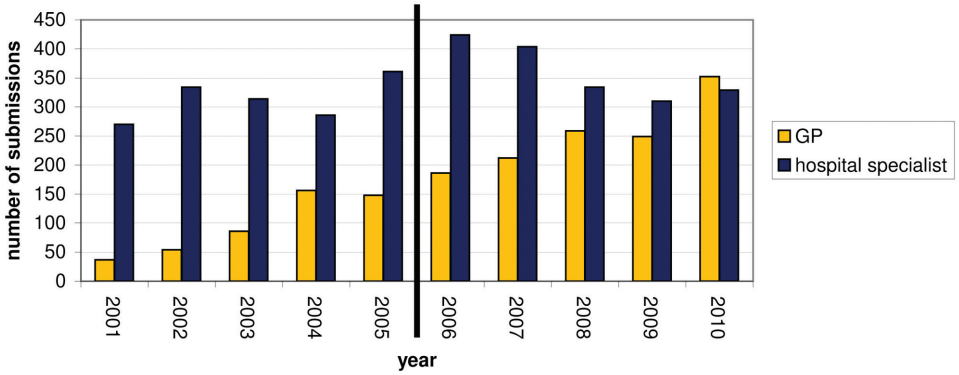
Malignant lesions: Between 2001 and 2010, 16,646 excisions of skin malignancies were submitted to the laboratory. Almost 17.5% of these were submissions by GPs. Both the submissions from GPs as well as from hospital specialists showed an increase, although the increase was larger for the GPs (Fig. 4). An increase in skin tissue samples submitted by GPs was observed for all skin malignancies.

Figure 4: Malignant skin tissue sample submissions by GPs and hospital specialists. (bold vertical line = introduction of 2006 contract)



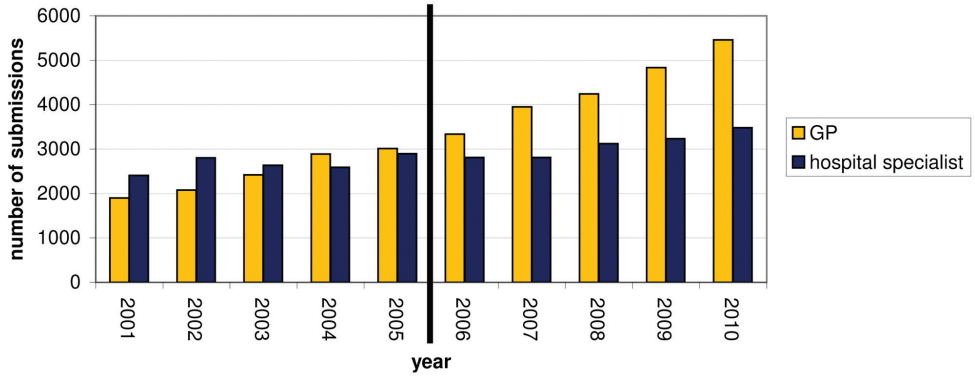
Premalignant lesions: GPs submitted 34.1% of the 5,105 premalignant excisions to the laboratory. As shown in Figure 5, the number of submissions by GPs increased over the years, but the number of submissions by specialists reached a maximum of 424 submissions in 2006 and subsequently decreased. In 2010, 51.7% of the premalignancies were submitted by GPs.

Figure 5: Premalignant skin tissue sample submissions by GPs and hospital specialists. (bold vertical line = introduction of 2006 contract)



Benign lesions: More than 54% of the 62,912 benign lesions were submitted by GPs. The submissions of GPs nearly tripled over the study period (Fig. 6). Nevertheless, the relative amount of benign lesion submissions by GPs remained equal: in 2005 87.7% of the lesions was benign and in 2010 86.7%.

Figure 6: Benign skin tissue sample submissions by GPs and hospital specialists. (bold vertical line = introduction of 2006 contract)



DISCUSSION

Summary

This retrospective study shows that during the last decade an increasing number of skin tissue samples were submitted for histopathological analysis by both GPs and hospital specialists. This increase was more pronounced for GPs than for hospital specialists. The study also suggests a lowered threshold among GPs to perform excisions after the introduction of the new contract, witnessed by the upward inflexion in trend for the number of skin tissue sample submissions by GPs after 2006. Nonetheless, the proportion of benign lesions, and therefore the benign / malignant ratio, remained stable. No, compensatory, change in trend for the number of skin tissue samples submissions by hospital specialists was seen.

Strengths and limitations

A major limitation of this study is that only skin tissue samples submitted for histopathological analysis were considered for analysis. This may not coincide with the real number of excisions performed. We do not know how many skin tissue samples were not submitted to the laboratory for analysis and despite the recommendation to submit all skin tissue samples for histological analysis, we know from previous studies that this does not always happen.[10-12] We also excluded all re-excisions because we did not assume those to be due to the incentive to excise but rather, for example, due to an incomplete previous excision. This exclusion was based on the sample encryption. However, during the first years only a few skin tissue samples were classified as being a re-excision. That is almost certainly an underestimation of reality. This factor might have resulted in an overestimation of the number of skin tissue sample submissions in the first years. A further possible confounder is that due to the payment agreements, GPs sometimes submitted two or more submissions in one bottle. These were registered as being just one sample and this might have caused an underestimation of the total number of submissions. Also, some skin lesions were coded and therefore analysed as being malignant and premaligant. On balance, however, we believe that this study is large enough for such effects to be mitigated and so any incorrect registrations will have a limited effect. Furthermore, the analysis of skin sample submissions was based on annually accumulated information, as no monthly information was available for analysis. We were therefore unable to pinpoint the exact month(s) in which this change in trend for GPs took place. Nevertheless, this change in trend occurred somewhere between 2006 and the end of 2007 and we believe that this is most likely a direct and/or deferred effect from the new 2006 financial contract.

Comparison with existing literature

A similar increase in skin tissue sample submissions was seen in several studies in the UK following a comparable financial contract.[3-7] However, comparison with a control group is

required to establish a causal relationship between a financial contract and the change in trend for the number of skin sample submissions by GPs. Neither the UK studies nor our study had a control group. In addition, some of the UK studies also suggested that the proportion of benign lesions did not change as a consequence of the contract.[2, 4-6] Our study differed, however, from the UK studies that used smaller study populations and shorter observation periods. Consequently, the UK studies may have missed a pre-existing trend and the increase they observed may have been inadvertently attributed to the putative effects of implementing the financial contract while our study looked at a period of 10 years and showed a significant upward inflexion in trend after the introduction of the new financial contract.

Implications for practice and research

In our study we demonstrated a steady increase in skin tissue sample submissions from 2001 onwards, reflecting the increasing demand on care for skin lesions. Probably, this is the result of various public campaigns[13, 14] and an increased incidence of skin malignancies in the Netherlands.[15, 16] The increase was significantly more pronounced for GPs than for hospital specialists. Our study also suggests a lowered threshold among GPs to perform excisions after the introduction of the new contract. However, no parallel compensatory change in trend was shown for hospital specialists, which might indicate that no substitution from secondary care to primary care has taken place. However, since the proportion of benign lesions in the GP submissions remained equal over the years, we think that the lowered threshold by GPs to perform excisions after the new contract was not due to a widening of the range of indication for excision, such as also including evident benign lesions. Further research, using a control group, is necessary to determine the true impact of a financial incentive on minor surgery in both primary and secondary care. Important outcome measures should be: cost-effectiveness and patient satisfactory.

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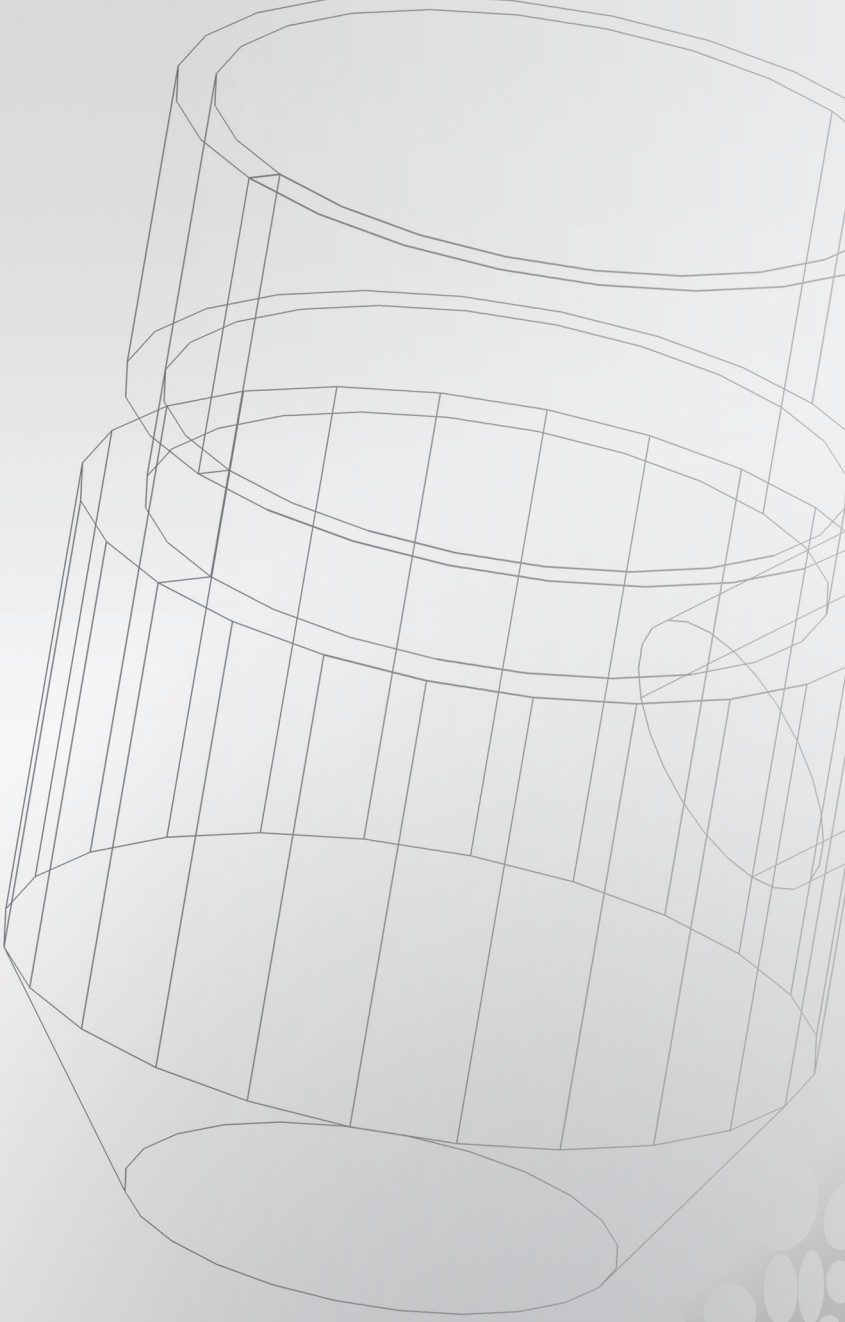

Chapter 4

Diagnostic accuracy and cost-effectiveness of dermoscopy in primary care: a cluster randomised clinical trial

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ABSTRACT

Background The dermoscope improves general practitioners' (GP) sensitivity for melanoma. However, diagnostic accuracy (DA) and cost-effectiveness of the dermoscope in primary care for the evaluation of all skin lesions suspected of malignancy is unknown.

Objectives To determine the DA and cost-effectiveness of the dermoscope in primary care for skin lesions suspected of malignancy.

Methods In a cluster randomised clinical trial 48 Dutch general practices were randomised to either intervention group using a dermoscope or control group using only naked-eye examination. 194 lesions from 170 patients in the intervention group and 222 lesions from 211 patients in the control group were analysed for DA and cost-effectiveness.

Results The percentage of correctly diagnosed lesions in intervention group and control group was 50.5% and 40.5% respectively. This was 61.5% and 22.2% for melanomas. In the intervention group 3 malignancies were treated with the expectative treatment option compared to none in the control group. The odds ratio (OR) of a correct diagnosis in the intervention group, compared to control group, was 1.51 (95% CI: 0.96-2.37) p = 0.07. Consequently, the relative risk was 1.25. The incremental cost-effectiveness ratio was €89 (95% CI -€60 to €598), indicating that using a dermoscope costs an additional €89 for one additional correctly diagnosed patient. Additional analyses showed better effects of dermoscopy compared to the control group for 98% of the bootstrap resamples.

Conclusions The probability of a correct diagnosis was 1.25 times higher using a dermoscope than without a dermoscope. Although this difference is marginally not statistically significant, dermoscopy in general practice appears to be cost-effective. We therefore think that GPs should be trained to use a dermoscope, although they should realise that even with the use of a dermoscope not all lesions will be diagnosed correctly.

INTRODUCTION

Skin cancer incidence is rising.[1-5] Currently, in the Netherlands, one in six people will develop skin cancer [6] and there is no prospect of an end to the increasing number of skin cancer patients.[7] This skin cancer epidemic will put an heavy burden on healthcare services and healthcare costs.[4, 6, 7] In the Netherlands, where the general practitioner (GP) has a gatekeeper role, the majority of lesions are initially evaluated by the GP. The skin lesions GPs are consulted for can be pigmented as well as non-pigmented and, in primary care, most are benign. It is the challenge for the GP to diagnose skin cancer as early as possible, while preventing unnecessary excisions and referrals to secondary care. To do so, cost-effective algorithms and tools are needed with a high diagnostic accuracy (DA).

In secondary care the dermoscope has been shown to improve the DA of melanoma by 49% for experienced examiners[8] and might add useful information when it comes to the diagnosis of non-melanocytic lesions.[9] On the other hand, the use of a dermoscope by untrained dermatologists reduces the sensitivity for melanoma by 10%.[10] In primary care, only a few studies on dermoscopy have been performed. These showed a 13-16% increase in the sensitivity for melanoma [11, 12] and a 25% better triage of skin lesions suggestive of skin cancer [13] compared to naked-eye examination alone. In the study of Argenziano et al., many non-melanoma skin cancers were also correctly diagnosed when using the dermoscope.[13] Nonetheless, clear evidence of the usefulness of the dermoscope in primary care for diagnosing the entire spectrum of lesions suspected for skin cancer, pigmented as well as non-pigmented, is still lacking. And although it is referred to as a fairly inexpensive tool for melanoma detection[14], the cost-effectiveness of the dermoscope in primary and secondary care has not been studied before.

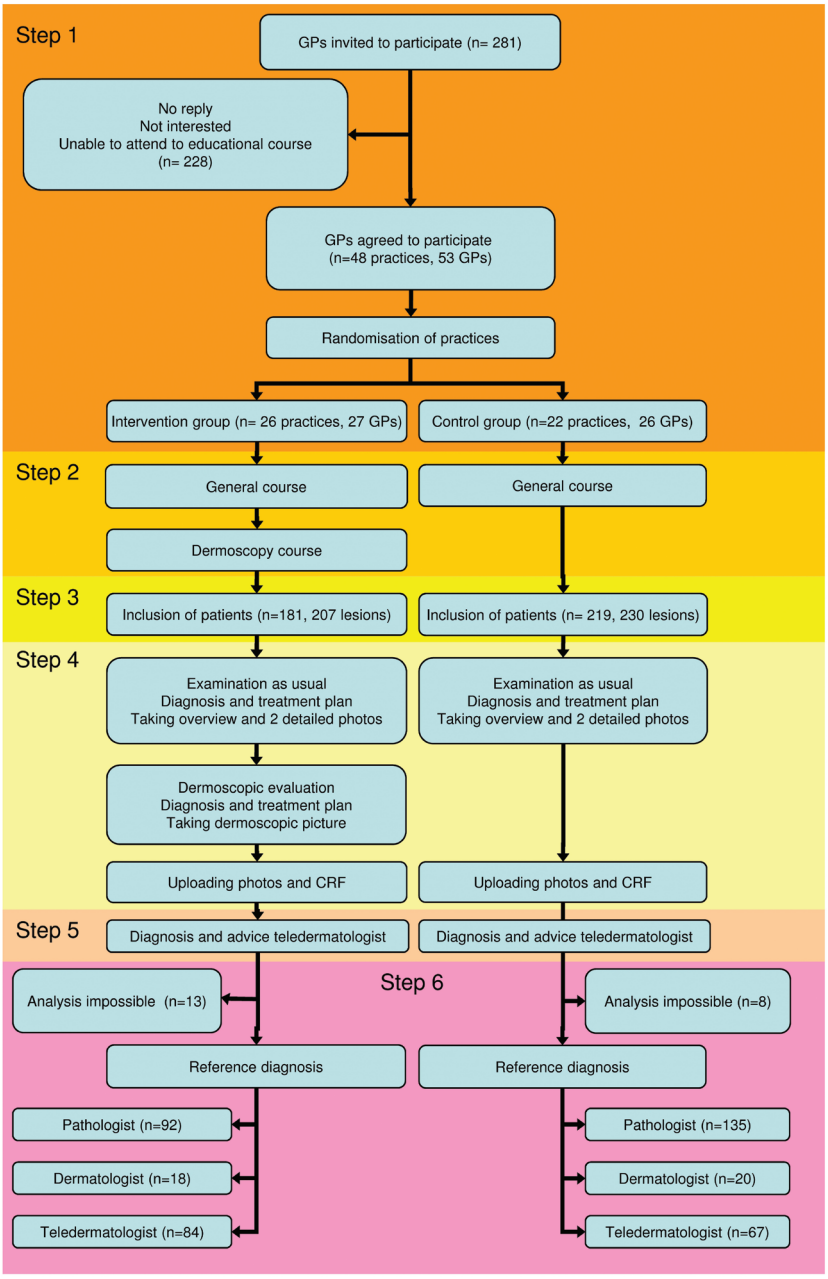
Therefore, the aim of this study is to determine the DA of the dermoscope in primary care by assessing its DA for all suspected skin lesions according to the GP and to explore its cost-effectiveness.

PATIENTS AND METHODS

Study design:

The Optoderma study was set up as a cluster randomised clinical trial conducted in primary care. Cluster randomisation was chosen to avoid contamination, as a possible learning effect of the dermoscope on routine examination by the GP cannot be excluded when evaluating a patient of the control group. The study was registered in the Dutch National Trial Registry (www.trialregister.nl, number NTR 2319) and approved by the Medical Ethical Board of the University Medical Center Groningen (UMCG). The design consists of six steps. (Fig. 1)

Figure 1: The study design



Step 1: recruitment and allocation of practices. Step 2: education of GPs. Step 3: patient inclusion Step 4: evaluation skin lesion + treatment. Step 5: teledermatology. Step 6: determination of reference standard diagnosis.

Step 1: Recruitment and allocation of GPs and practices

An invitation letter was sent to 282 GPs in the north-eastern part of the Netherlands (i.e. the provinces of Groningen, Friesland, Drenthe and Overijssel). Only GPs working at least three days per week and who were able to attend to the educational courses were eligible for participation. In total 53 GPs from 48 practices were willing to participate. The practices were matched based on their practice size and computerised randomisation to either a control group or an intervention group took place within these matches. Randomisation was performed by an independent staff member of the Trial Coordination Center of the UMCG. GPs as well as researchers were aware of the allocation.

Step 2: Education of GPs

All 53 GPs followed a 4-hour general course given by dermatologists from the UMCG. This course included modules about the epidemiology of suspected skin lesions in primary care, the recognition of lesions suggestive for skin cancer and the photography of skin lesions. At the end of this general course a test was conducted, which revealed no significant differences in knowledge between GPs from the intervention group and the control group.

The 27 GPs from the intervention group also attended a 6-hour course on dermoscopy given by Dutch dermoscopy experts. In this additional course the focus was on distinguishing melanocytic and non-melanocytic lesions and the use of the 7-point checklist. This checklist consists of seven features that must be scored during dermoscopy; a score ≥ 3 indicates that a lesion is suggestive of melanoma.[15] Other modules in the course were: the dermoscopic features of non-melanocytic lesions and dermoscopic photography. The photography recommendations given in the general course were derived from teledermatology guidelines[16] complemented with recommendations from the medical photographer of the Department of Dermatology of the UMCG. In the dermoscopy course the photography module was lectured by the medical photographer.

Step 3: Patient inclusion

Patients were included by their own GP when they consulted him/her for a skin lesion.

Inclusion criteria were:

- patients presenting in general practice with a suspected lesion of the skin according to the GP;
- age 18 years or older;
- informed consent.

Exclusion criteria:

- currently being treated because of a skin malignancy;
- suffering from severe illness according to the GP.

Step 4: Evaluation of skin lesion and treatment:
Evaluation: All patients included in the study underwent the routine naked-eye examination from their GP combined with medical history. Photos, one overview and two detailed, were taken and the online case report form (CRF) asking for age, gender, medical history, diagnosis and treatment plan was filled in. In the intervention group, the GPs subsequently evaluated the lesions with the dermoscope. They then took a dermoscopic photo and filled in a second part of the CRF. In this second part of the CRF the diagnosis and treatment plan after dermoscopy had to be registered.
Treatment: In the control as well as the intervention group, all patients were expected to be treated as stated in the CRF. For the intervention arm this meant the treatment stated after dermoscopy. Treatment options were: expectative, excision / incision biopsy by GP, referral to a dermatologist or teledermatology by the GPs own teledermatology centre. The GP also had the option to fill in another treatment option when the above mentioned options were considered inappropriate.

Step 5: Teledermatology
All CRFs with corresponding photos were evaluated by two out of four dermatologists of the Department of Dermatology of the UMCG. Diagnosis was based on consensus between both dermatologists. The GP received a digital reply, which only stated whether the lesion was benign, pre-malignant or malignant. This reply also included a treatment advice; GPs were free to follow this advice. This form of minimised reply was chosen to prevent bias due to a learning effect while on the other hand preventing a wrong treatment in case of a malignancy.

Step 6: Determination of reference diagnosis
As obtaining a histological diagnosis of every lesion, which would mean biopsy or excision of all lesions, is ethically unacceptable the following reference standard diagnoses were used in hierarchical order:
1 diagnosis of the pathologist in case of biopsy or excision (by either the GP or dermatologist);
2 diagnosis of the dermatologist in case of referral;
3 diagnosis of our trial teledermatologist.
After 8, 13 and 19 months the GPs were asked, if applicable, for the diagnosis as stated under 1 and 2.

Outcome measures

The main outcome measures were DA, defined as the odds ratio of correctly diagnosed lesions in the intervention group compared to the control group, and cost-effectiveness.

Data collection and handling

Data, received through the digital CRF, were automatically entered into an online, password-protected, database. The uploaded photos were only visible to the study dermatologists, the submitting GP was visible for researchers and study dermatologists. However, patient information was anonymous using a patient number which was held by, and therefore only to be tracked by, the submitting GP. Diagnosis and treatment advice as given by our study dermatologists was also entered into this online database. At the end of the study period, the online database was imported into a SPSS file and reference diagnoses, as retrieved from the GP, were added.

Sample size calculation

Based on unpublished data from our general practice registration network we estimated an average of 30 patients per year to visit their GP for a, skin lesion suspected for malignancy. Based on expert opinion we assumed the diagnosis being clearly benign in 20 lesions, uncertain in 5 lesions, premalignant in 2 lesions and malignant in 3 lesions. Therefore, approximately 10 patients per year per practice would be eligible for inclusion. We expected a difference in the percentage of correctly diagnosed lesions of 20% (45% and 65% in the control and intervention group respectively). Given a significance level of 5% and power of 80%, 105 patients in both control and intervention group were needed. To correct for independence, because of cluster randomisation, we assumed a standard deviation in the effect of the practices on the outcome of 0.1 resulting in a correction factor of 1.71.[17] Therefore, the total number of patients needed would be 357, with an estimated participation of 75% we would need 476 patients to be included by their GP. Assuming an inclusion period of one year, we would need 48 GPs with an average practice size.

Materials

The GPs of the intervention group used a Sony Powershot W290 camera. As dermoscope a Dermlite II PRO HR was used, which could be connected to the camera with a Sony Powershot VAD-WG lens adaptor. The GPs of the control group used a digital camera that had to meet the standard criteria for teledermatology; the main criterion being a minimum resolution of 1.2 megapixels.

Statistical analyses

For both the intervention group and the control group, descriptive analyses were used to describe the number of patients, lesions, percentage of correctly diagnosed lesions and the treatment as stated by the GP, i.e.: expectative, excision / incision biopsy, referral to secondary care or teledermatology outside the study and the costs.

Diagnostic accuracy

For the intervention group the diagnosis of the GP after examination with the dermoscope was used and for the control group the diagnosis after routine naked-eye examination. This was before the GP received a digital reply from our study dermatologists.

The analysis of a cluster randomised trial requires the implementation of statistical methods that correct for the clustering of information. Therefore, for the analysis of clustered data in this study MLwiN (version 2.25) was used. Binomial multilevel analysis was conducted to determine the ratio between the control and intervention groups. Two levels were identified; ´patient´ was defined as the first level and ´practice´ was defined as second level. The quasi-likelihood estimation procedure was used to estimate the parameters of the multilevel model. The outcome variable is represented by the logit of the probability (i.e. natural log of the odds) of intervention/control group. The regression coefficient was subsequently transformed into an odds ratio (OR) by taking the exponent [regression coefficient] and presented with 95% confidence intervals (95% CI). Significance of the beta-coefficient was based on the Waldtest. A p-value < 0.05 was considered significant. Additionally, the OR was converted into a relative risk (RR) for obtaining a correct diagnosis based on the following equation:

$RR = OR / [1 + CER(OR-1)]$in which CER = control event rate.

Cost-effectiveness analysis

Costs included were: consultation fees for GP and hospital specialist, treatment costs (treatment as stated by the GP) i.e. pathology services and teledermatology, purchase of the dermoscope and the educational courses for the GPs. These are detailed in Table 1. Costs were calculated from the healthcare perspective and since the time horizon was shorter than one year, costs were not discounted. The incremental cost-effectiveness ratio (ICER) was computed by comparing the direct medical costs, based on additional costs per extra correctly diagnosed patient, of the intervention group with the control group. A scatter diagram with the four quadrants of the cost-effectiveness analyses plane was computed to obtain insight in the uncertainty surrounding the point estimate of the ICER. This was done using bootstrap resampling with 5000 replications, and also yielded the95% CI. In addition, a cost-effectiveness acceptability curve (CEAC) was generated representing the chance that dermoscopy is cost-effective over a range of thresholds.

Table 1: Types of costs, determination, unit and unit prices.

	Determination	Unit	Unit price (€)
Consultation fee GP	Cost manual*	Visit	28
+ minor surgery	Cost manual*	Visit	28
+ teledermatology	Tariffs†	Session	55
Consultation fee dermatologist	Cost manual*	Visit	110
Pathology services	Tariffs†	Session	87
Dermoscope	True investments: Interest and debits (10 years)	Session	15
Educational costs (control group)	True investments (5years)	Visit	15
Educational costs (intervention group)	True investments (5years)	Visit	30

* Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. [Manual for cost analysis in healthcare.]. Dutch Health Insurance Board; Actualized version 2010.
† The Dutch Healthcare Authority. Available at: http://www.nza.nl/regelgeving/tarieven/. , 2012.

RESULTS

After randomisation, but before the educational courses, five GPs (two practices) from the intervention group and three GPs (three practices) from the control group withdrew participation due to logistical reasons. To ensure sufficient patient inclusion, we replaced them with new GPs. This resulted in the participation of 53 GPs from 48 practices. All GPs followed the educational courses.

Patients were included from April 2010 until the calculated sample size was reached in September 2011. In total 437 lesions from 400 patients were included by respectively 22 GPs (21 practices) and 21 GPs (18 practices) from the intervention group and the control group. Of these lesions, 21 lesions from 19 patients had to be excluded; 19 because the patient had an age <18 years and 2, one in each group, because no reference standard diagnosis was available. (Fig. 1) Practice, patient and lesion characteristics are described in Table 2. More than 20% of the included lesions concerned skin malignancies. The treatments patients received, as stated by the GP, are shown in Table 3.

Table 2: Characteristics of GPs, patients and lesions. Values are numbers (%) unless stated otherwise.

	Intervention group		Control group	
Practice characteristics				
Number of practices	26		22	
Number of GPs	27		26	
Sex, female	3		12	
Patient characteristics				
Patients	170		211	
Sex, female	116		130	
Mean age in years (SD)	53.2 (16.9)		54.7 (17.6)	
Lesion characteristics				
	In database†	Correctly diagnosed	In database†	Correctly diagnosed
Melanoma	13	8 (61.5)	9	2 (22.2)
Squamous cell carcinoma	2	1 (50.0)	5	0 (0.0)
Basal cell carcinoma	26	20 (76.9)	31	26 (83.9)
Actinic keratosis	21	13 (61.9)	27	11 (40.7)
Normal naevus	58	26 (44.8)	52	24 (46.2)
Atypical naevus	9	4 (44.4)	9	5 (55.6)
Verruca seborrhoica	35	23 (65.7)	45	18 (40.0)
Angioma	3	3 (100)	6	0 (0.0)
Lentigo	6	0 (0.0)	8	2 (25.0)
Fibroma	3	0 (0.0)	4	1 (25.0)
Kerato-acanthoma	3	0 (0.0)	1	0 (0.0)
Sebaceous gland hyperplasia	1	0 (0.0)	0	-
Other	14	0 (0.0)	25	1 (25.0)
Total number of lesions	194	98 (50.5)	222	90 (40.5)

† according to reference standard diagnosis

Table 3: Treatment as stated by GP. Values are numbers (percentages).

	Intervention group	Control group
Watchful waiting	81 (41.5)	53 (23.8)
Excision	69 (35.4)	90 (40.4)
Incision biopsy	3 (1.5)	11 (4.9)
Referral to secondary care	34 (17.4)	50 (22.4)
Teledermatology	7 (2.6)	13 (5.8)
Other / nitrogen	4 (1.5)	6 (2.7)

Diagnostic accuracy

The overall OR of a correct diagnosis in the intervention group, compared to control group, was 1.51 (95% CI: 0.96-2.37) p = 0.07. This coincided with a RR of 1.25, meaning that in our population the probability of obtaining a correct diagnosis using a dermoscope was 1.25 times higher than without a dermoscope.

The percentage of correctly diagnosed lesions in the intervention group and the control group was 50.5% and 40.5% respectively. However, this percentage varied between the different types of lesions. The difference in the percentage of correctly diagnosed melanomas was striking. This was 61.5% in the intervention group compared to 22.2% in the control group. This lead to an OR of 5.52 (95% CI: 0.76+39.91) (Table 2) However, in the intervention group 3 malignancies (1 melanoma, 1 squamous cell carcinoma, 1 basal cell carcinoma) were treated with the expectative treatment option compared to none in the control group.

Cost-effectiveness

There was a difference in costs of €892 in favour of the control group. Given the difference in the percentage of correctly diagnosed lesions of 10%, an ICER of €89 was calculated with a 95% CI of -€60 to €598. This indicates that using a dermoscope, it would cost €89 for one additional correctly diagnosed patient. Based on the analyses, 98% of the bootstrap resamples fell into the quadrants on the right side of the Y-axis. This means that these resamples have better effects compared to the control group. In 91% of these (more effective) estimates, costs were higher and in 7% the costs were lower. (Fig. 2) The CEAC shows that investing €1000 would result in an almost 100% chance of the dermoscope being cost-effective. (Fig. 3)

Figure 2: Scatter diagram of costs and benefits (percentage gain of DA) based on bootstrap analysis.

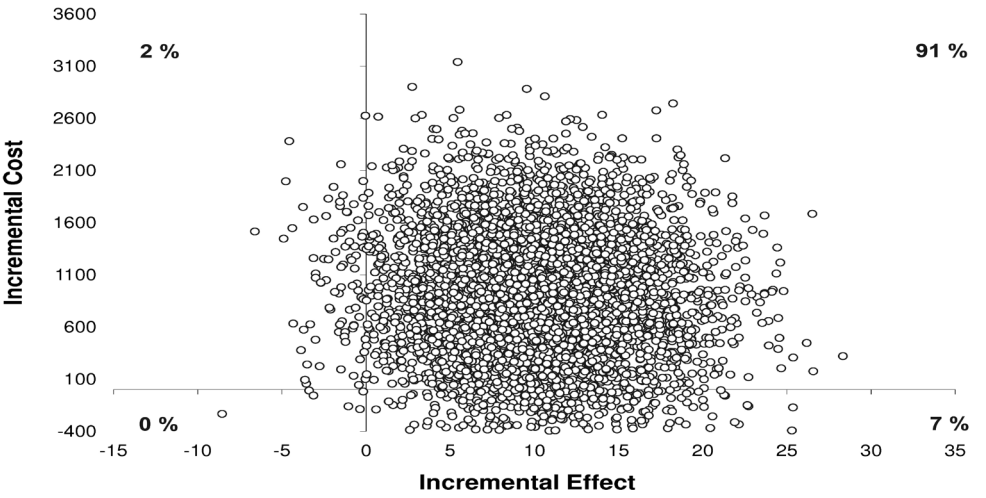
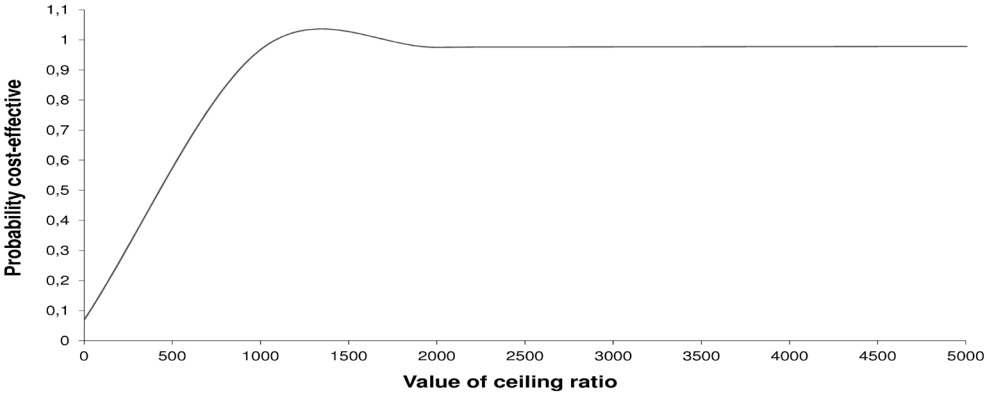


Figure 3: Cost-effectiveness acceptability curve showing the probability of the dermoscope being cost-effective. X-axis shows the threshold for willingness to pay (€).



DISCUSSION

Main findings

The OR of a correct diagnosis using a dermoscope, compared to naked-eye examination alone, was 1.51 (95% CI: 0.96-2.37). This coincided with a RR of 1.25 meaning that the probability of a correct diagnosis using a dermoscope was 1.25 times higher than without a dermoscope. However, this was not statistically significant. Furthermore, we found a remarkable difference in the percentage of correctly diagnosed melanomas of 39.3% in favour of the dermoscope. Additionally, our study showed that dermoscopy in a primary care setting appears to be cost effective with a low ICER of €89, meaning that the additional costs would be €89 per additional correctly diagnosed patient. This low ICER was mainly a result of the lower treatment costs in the intervention group, due to less excisions and referrals to secondary care.

Comparison with other studies

In secondary care, the dermoscope has already been shown to increase diagnostic accuracy for melanoma[8, 18] and its usefulness has increasingly been described for the diagnosis of non-pigmented skin tumours.[19-21] In primary care, studies have shown that the dermoscope increases sensitivity for melanomas by up to 15.6% and also an improvement in the diagnosis of non-melanoma skin cancers has been observed.[11-13] We found a difference of 39.3% for melanomas. However, this was based on only 22 melanomas. In our study, the OR of a correct diagnosis using a dermoscope, compared to naked-eye examination alone was 1.51 (95% CI: 0.96-2.37) p=0.07. However, this was for all possible malignant skin lesions (pigmented and non-pigmented). We opted for this broad spectrum of possible malignant skin lesions as we think this is a more accurate reflection of daily practice. The only other randomised clinical trial of dermoscopy in primary care using 'in clinic' evaluation of patients by Argenziano et al.[13] also looked at possible malignant skin lesions. However, their outcome measure was referral sensitivity based upon the differentiation between banal lesions and lesions suggestive of skin cancer. This is different from our outcome measure of diagnostic accuracy. Therefore, the increase of 25% in referral sensitivity is not comparable with our increase in the percentage of correctly diagnosed lesions.

Strengths and weaknesses

We conducted a large cluster randomised clinical trial in primary care. However, when the power analysis was conducted, we assumed the difference in the percentage of correctly diagnosed lesions between the intervention and control group to be 20%. In our results, however, this was only 10%. The sample size was therefore too small to demonstrate a significant difference between the two groups and in retrospect the study may have been underpowered. Nevertheless, we believe that a difference of 10% is clinically significant.

Especially as the percentage of correctly diagnosed melanomas was 39% higher in favour of the intervention group. Nevertheless, a larger sample size in future research might reveal this clinically significant difference also to be statistically significant. As GPs are also responsible for the triage of patients an outcome measure as the percentage of correctly diagnosed malignancies is also important. In this study, however, the primary outcome measure was diagnostic accuracy. This was chosen because different kind of lesions call for different treatments and, therefore, a high diagnostic accuracy is important.

Considering the methods used in this study, only polarised dermoscopes were used. In contrast to non-polarised dermoscopes, no oil immersion has to be applied when using these dermoscopes. We anticipated that this would lower the threshold for the GP to use the dermoscope. However, polarised and non-polarised dermoscopes both have advantages and disadvantages.[22] The use of a non-polarised dermoscope might therefore lead to another diagnostic accuracy. Furthermore, the GPs in this study were trained to use the 7-point checklist. However there are other methods that might be easier to learn as they avoid the first step of making a distinction between melanocytic and non-melanocytic lesions.[9, 23] A future study should point out which of these methods is preferred for the examination of all, pigmented and non-pigmented possible malignant skin lesions.

For cost-effectiveness analyses we assumed dermoscopy training to be repeated once every 5 years but no study, in primary or secondary care, has yet determined how often this is actually required. Changing the frequency of training would of course change the ICER. Secondly, only direct medical costs were calculated and analysed but long-term medical costs, for instance the costs of misdiagnosing one skin cancer, could not be included as this would require a long follow-up. However, as the percentage of correctly diagnosed lesions in the intervention group was higher than in the control group we believe that including these costs would not change our conclusion that dermoscopy in primary care appears to be cost-effective.

Meaning of the study?

We could not establish a statistically significant added value of the dermoscope, which was probably because the sample size was too small. Future research with a larger sample size will therefore be necessary to determine the true added value of the dermoscope. Nonetheless, we believe that the, non-significant, difference found in this study is highly relevant as a correct diagnosis is important for a correct treatment. This is particularly true in the case of a melanoma, for which we found a difference of more than 39% in favour of using a dermoscope, as an early diagnosis and treatment can save a life. On the other hand, 3 malignancies in the intervention group were treated with the expectative treatment option compared to none in the control group. This might indicate that dermoscopy might lead to an overestimation of the diagnostic accuracy by the GP. Additionally, our study did show that the dermoscope

appears to be cost-effective in primary care. We therefore believe that GPs should be trained to use a dermoscope, although they should realise that even with the use of a dermoscope not all lesions will be diagnosed correctly.

Conclusions

Although in our population we found that the probability of a correct diagnosis using a dermoscope was 1.25 times higher than without a dermoscope, we could not establish a statistically significant added value of a dermoscope for all skin lesions suspected for malignancy. Nevertheless, dermoscopy appears to be a cost-effective diagnostic intervention in primary care.

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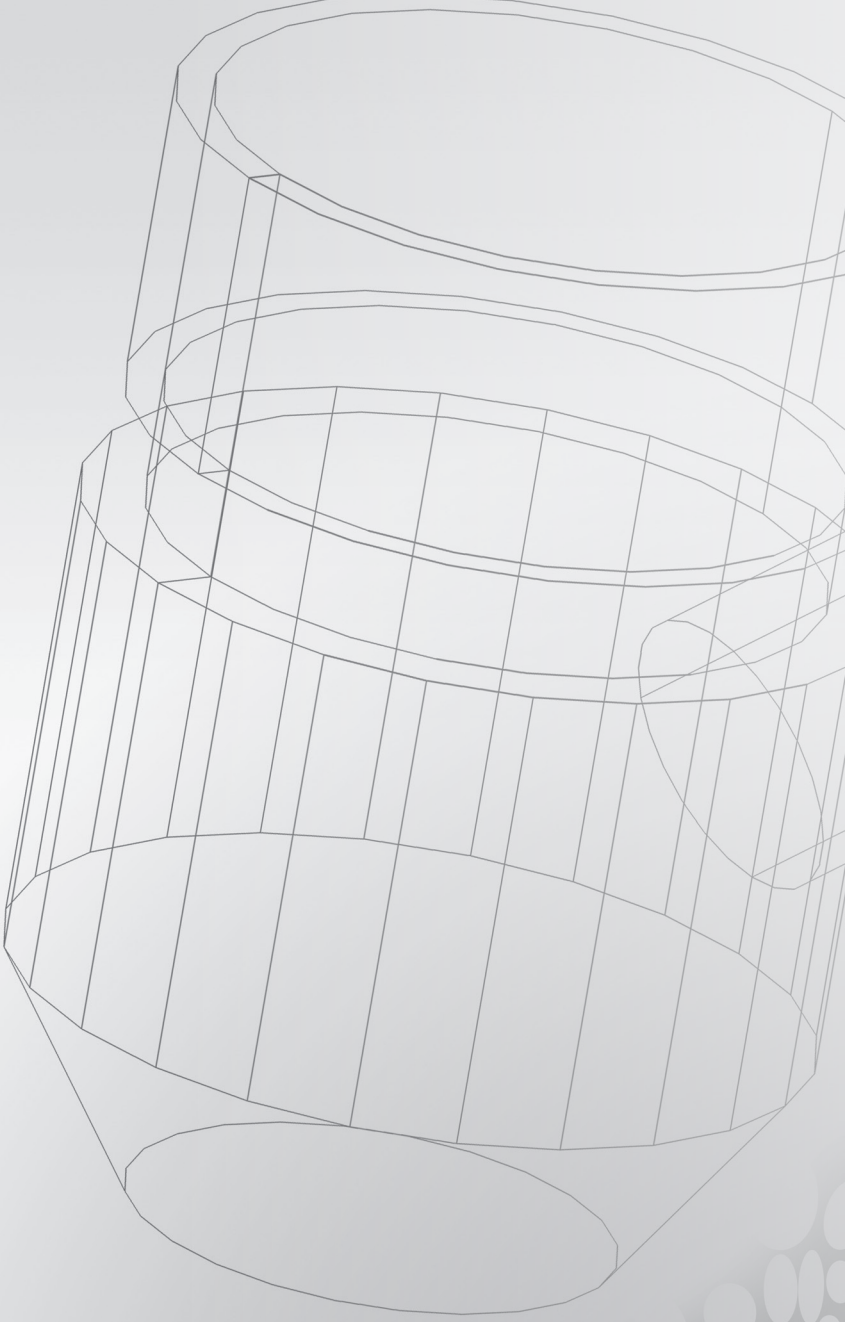


Chapter 5

The influence of dermoscopy on the diagnosis and treatment of benign and malignant skin lesions in general practice

INTRODUCTION

Previously, as described in Chapter 4, we performed a cluster randomised clinical trial which revealed that using a dermoscope in primary care appears to be cost-effective. Also, although it did not reach statistical significance, we found that within our study population the diagnostic accuracy (DA) for potentially malignant skin lesions was 10% higher when using a dermoscope compared to care as usual. In addition, by using a dermoscope the DA for melanoma was 39% higher. This increase in DA for melanoma is consistent with other studies performed in primary and secondary care settings.[1-3] However, one could also argue that the treatment of both benign and malignant lesions is just as important as diagnostic accuracy. Furthermore, with respect to both mortality and morbidity, it is particularly important that each (pre)malignancy is diagnosed correctly.

In this chapter, we re-evaluated the results of our cluster randomised clinical trial to determine whether using a dermoscope improves the ability of a general practitioner (GP) to accurately diagnose premalignant and malignant skin lesions. Furthermore, we examined the treatment received by patients with benign or malignant lesions.

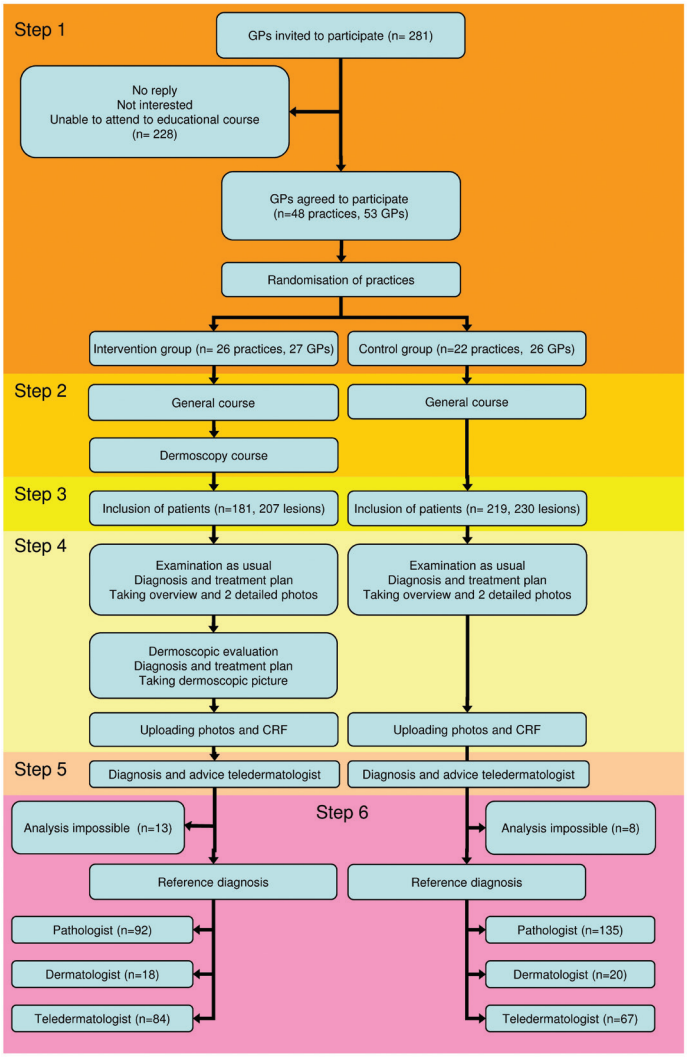
METHODS

Study design

This study was based on the results of a large trial to investigate the diagnostic accuracy (DA) achieved using a dermoscope in primary care. The design, inclusion criteria, and exclusion criteria of this study are described in detail in Chapter 4. In brief, the trial was a cluster randomised clinical trial in which the DA for GPs who used a dermoscope (referred to here as the intervention group) was compared to the DA of GPs who did not use a dermoscope (the control group). In addition, the cost-effectiveness of using a dermoscope was evaluated. After the practices were randomised, each GP attended an educational course regarding diagnosing skin cancer. The GPs from the intervention group were additionally trained in the use of a dermoscope. The lesions included in the study were pigmented or non-pigmented skin lesions that were determined to be potentially malignant by the evaluating GP. After the inclusion and examination of the patient, the GP completed an online case report form (CRF). This CRF was completed for each lesion as all lesions were diagnosed and assessed separately. The completed CRF, which included the GP's diagnosis and treatment, was uploaded to an online, password-protected database together with pictures of the lesion. In the intervention group, dermoscopic pictures were uploaded as well. The pictures and CRFs of all lesions were then evaluated by two teledermatologists from a study team that consisted of four teledermatologists. After evaluating the data, the teledermatologists entered their diagnosis and treatment advice into the database. Subsequently, the GP received only the

information regarding whether or not the lesion was potentially malignant together with the recommended treatment. To measure DA, the GP's diagnosis was compared to the reference standard diagnosis. This reference standard diagnosis was the diagnosis based upon (using a hierarchical order): the diagnosis of a pathologist, the diagnosis of a regional dermatologist, or the diagnosis of the study's teledermatologist. (Fig. 1)

Figure 1: The study design.



Step 1: recruitment and allocation of practices. Step 2: education of GPs. Step 3: patient inclusion Step 4: evaluation skin lesion + treatment. Step 5: teledermatology. Step 6: determination of reference standard diagnosis.

Main outcome measures

- The odds ratio (OR) of receiving a correct diagnosis for a (pre)malignant lesion using a dermoscope compared to care as usual.
- The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for (pre)malignant skin lesions in both the intervention and control groups.
- The absolute risk reduction realised by using a dermoscope with respect to: (1) malignant lesions that were incorrectly assigned to a watchful waiting approach (i.e. false negatives), and (2) benign lesions that were excised, biopsied or referred to secondary care.

Statistical analyses

Descriptive analyses were used to describe the number and relative percentages of the various reference diagnoses for the lesions in the patients assigned to the intervention and control groups. (Table 1)

OR, sensitivity, specificity, PPV and NPV of (pre)malignant lesions

To determine whether each lesion was benign or malignant, we used the reference standard diagnosis. Because some premalignant lesions require treatment such as referral to secondary care or excision, we pooled the premalignant and malignant skin lesions for calculating the OR, sensitivity, specificity, PPV and NPV. Both the reference standard diagnosis and the GP's diagnosis were categorised as either benign or (pre)malignant. Subsequently, the sensitivity and specificity (together with their corresponding 95% confidence intervals) of the (pre) malignant lesions in both the intervention and control groups were calculated. The PPV and NPV were also determined. Because this trial was cluster randomised, binary multilevel analysis (using MLwiN version 2.27) was conducted to determine the OR of obtaining a correct diagnosis for a (pre)malignant lesion using a dermoscope compared to care as usual. A quasi-likelihood estimation procedure was used to estimate the parameters of the multilevel model. The outcome variable is represented as the logit of the probability (i.e. the natural log of the odds) of intervention/control group. The regression coefficient was subsequently transformed into an odds ratio (OR) using the exponent [regression coefficient] and is presented with its 95% confidence interval (95% CI). The significance of the beta coefficient was determined using the Wald test; differences with a p-value <0.05 are considered to be significant.

Treatment of malignant lesions

For patients with a malignant lesion based on the reference standard diagnosis, we determined whether the patient was referred to secondary care or whether the lesion was excised or biopsied. In other words, we assessed the treatment as stated by the GP prior to receiving the advice of our study teledermatologist. Subsequently, the percentage of lesions that were

not referred, excised or biopsied was calculated in both the intervention and control groups, and an absolute risk reduction (with 95% CI) was calculated. In other words, we calculated the reduction in the risk of a patient with a malignant lesion incorrectly handled using a watchful waiting approach when using a dermoscope. Premalignant lesions were not included in this analysis, as there is currently an on-going debate regarding whether all premalignant lesions should be treated.

Treatment of benign lesions

Based on the reference standard diagnosis, we also classified the patients with benign lesions on whether they were initially referred to secondary care, whether their lesion was excised (or biopsied), or whether they were handled using a watchful waiting approach. Subsequently, the percentage of lesions that were not referred or excised was determined and the absolute risk reduction (with 95% CI) was calculated. In other words, we calculated the reduction in the risk that a patient with a benign lesion would be either referred to secondary care or have the lesion excised or biopsied.

RESULTS

From April 2010 through September 2011, data regarding 437 lesions were included by 22 and 21 GPs from the intervention and control groups respectively. Of these 437 lesions, 21 were excluded (19 patients were under the age of 18 and two had no reference standard diagnosis available). Thus, a total of 416 lesions were analysed (Figure 1). The distributions of the reference diagnoses in the intervention and control groups are presented in Table 1. In total, approximately 34% of the skin lesions were diagnosed as either malignant or premalignant.

Table 1: Summary of the reference standard diagnoses in the intervention and control groups. The reported values are the number of lesions (% of total).

	Intervention group	Control group	Total
All lesions	194 (46.6%)	222 (53.4%)	416
Benign	130 (47.8%)	142 (52.2%)	272
Premalignant	23 (39.7%)	35 (60.3%)	58
Malignant	41 (47.7%)	45 (52.3%)	86
Melanoma	13 (59.1%)	9 (40.9%)	22
Squamous cell carcinoma	2 (28.6%)	5 (71.4%)	7
Basal cell carcinoma	26 (45.6%)	31 (54.4%)	57

OR, sensitivity, specificity, PPV and NPV of (pre)malignant lesions

The combined number of premalignant and malignant lesions diagnosed in this study based on the standard reference diagnosis was 80 in the control group and 64 in the intervention group. The sensitivity, specificity, PPV and NPV for detecting a (pre)malignant lesion are presented in Table 2. The OR of obtaining a correct diagnosis of a (pre)malignant lesion using a dermoscope (i.e. in the intervention group) relative to care as usual (i.e. the control group) was 1.35 (95% CI: 0.52 – 3.54) (p=0.54).

Table 2: Sensitivity, specificity, PPV and NPV of (pre)malignant lesions.

	Intervention group	Control group
Sensitivity	82.8% (95% CI: 71.8% - 90.1%)	77.5% (95% CI: 67.2% - 85.3%)
Specificity	78.5% (95% CI: 70.6% - 84.7%)	81.0% (95% CI: 73.8% - 86.6%)
PPV	65.4% (95% CI: 54.6% - 74.9%)	69.7% (95% CI: 59.5% - 78.2%)
NPV	90.3% (95% CI: 83.4% - 94.5%)	86.5% (95% CI: 79.6% - 91.3%)

95% CI = 95% confidence interval. PPV = positive predictive value. NPV = negative predictive value

Treatment of malignant lesions

For three of the 86 malignant lesions (45 lesions in the control group and 41 lesions in the intervention group), the GP elected to use a watchful waiting approach. All three lesions were in the intervention group and included one melanoma, one squamous cell carcinoma and one basal cell carcinoma. The difference in absolute risk obtained from using a dermoscope was -7.3% (95% CI: -19.5% - 1.9%). For another four lesions in the intervention group (three basal cell carcinomas in the control group and one melanoma), teledermatology was used. In the control group, one basal cell carcinoma (which was correctly diagnosed by the GP) was initially treated using liquid nitrogen. All other lesions were either excised or biopsied (22 from the control group and 21 from the intervention group) or referred to secondary healthcare (19 in the control group and 16 in the intervention group) for further evaluation and treatment.

Treatment of benign lesions

This study included 272 benign lesions. For 47 of the 142 lesions in the control group (33.1%) and 67 of the 130 lesions in the intervention group (51.5%), a watchful waiting approach was used. All of the remaining benign lesions were treated using an intervention such as teledermatology, excision or biopsy, or referral to secondary healthcare (Table 3). Thus, the use of a dermoscope by the GP led to significantly fewer interventions, with an absolute risk reduction of 18.4% (95% CI: 6.7%-29.5%).

Table 3: Treatment of benign lesions as stated by GP. The reported values are numbers of lesions (% of total).

	Intervention group	Control group
Watchful waiting approach	67 (51.5%)	47 (33.1%)
Excision	40 (30.8%)	66 (46.5%)
Incision biopsy	1 (0.8%)	4 (2.8%)
Referral to secondary healthcare	16 (12.3%)	18 (12.7%)
Teledermatology	4 (3.1%)	5 (3.5%)
Other treatment (e.g. liquid nitrogen)	2 (1.5%)	2 (1.4%)
Total	130 (100%)	142 (100%)

DISCUSSION

Main findings

Compared to care as usual, the OR for correctly diagnosing a (pre)malignant lesion using a dermoscope was 1.35 (95% CI: 0.52–3.54, p=0.54). Thus, dermoscopy did not significantly increase the rate of correct diagnosis of (pre)malignant skin lesions by the GP. In the intervention group, who used the dermoscope, three malignant lesions were incorrectly handled using a watchful waiting approach. In contrast, no malignant lesions in the control group were incorrectly handled using a watchful waiting approach. However, based on the analyses of the absolute risk reduction, this difference was not found to be significant. The primary advantage of the GP using a dermoscope was that significantly fewer benign lesions were referred or excised.

Comparison with other studies

Three other studies regarding the use of dermoscopy by primary care physicians have been published[2-4] and only the study by Argenziano et al. was a clinical trial.[4] The outcome measure used in this study was referral accuracy in which the identification of a lesion as either banal or suggestive of skin cancer was compared to the dermatologist's assessment. The other two studies were limited to pigmented lesions and melanomas.[2, 3] Thus, their approach differed from our primary outcome measures. Also, different algorithms were used in the various studies and this may have affected the diagnostic accuracy.[5] Nevertheless, some interesting comparisons can be made.

In the study by Argenziano et al., 56.6% of the malignant lesions in the care as usual group and 84.6% of the malignant lesions in the dermoscopy group were correctly diagnosed as being

suggestive of skin cancer (p=0.002). In our study, the sensitivity for correctly diagnosing (pre) malignant lesions was 77.5% for the care as usual group and 82.8% for the dermoscopy group. Thus, the sensitivity achieved from using a dermoscope was quite similar in both studies even though the absolute gain in our study was not as high as in the study of Argenziano et al.. Why the sensitivity in the control groups differed between the two studies is unclear, but may be due to the fact that GPs in our study received more training in the basic clinical criteria used for diagnosing skin cancer than the GPs in Argenziano et al.'s study (4 hours versus 2 hours, respectively). Nevertheless, these results demonstrate that when determining the benefit of using a diagnostic tool, the accuracy of the control group largely determines the magnitude of that benefit.

Secondly, in our study, 100% and 92.7% of the malignant lesions in the control and intervention groups, respectively, were either excised or referred to secondary care. In the study by Argenziano et al., high negative predictive values were observed (with NPV in the control and intervention groups of 95.8% and 98.1%, respectively) based on referral sensitivity.[4] In a different study, 97.1% of melanomas were correctly treated.[2] However, although our control group performed better and our intervention group performed somewhat worse than the two previous studies, all of the reported rates were based on relatively few malignant lesions. For example, in our study, the difference in the incidence of incorrect treatment (7.3%) was based on only three malignancies. However, given that all rates are well above 90%, both care as usual and dermoscopy seem to have a low probability of incorrect treatment of malignant skin lesions.

In addition, we found that dermoscopy significantly reduced the number of interventions for benign lesions. A similar result was reported previously with respect to pigmented lesions.[2] Likewise, a large prospective study of a skin cancer database revealed that the number needed to treat, that is the number of excisions needed for the excision of one melanoma, decreased when using a dermoscope. However, the use of a dermoscope in this study was tightly correlated to the GP's practice type (i.e. a general practice, a general practice with a focus on skin cancer, or a skin cancer practice), and this could have affected the outcome.[6] In our study, we did not analyse the data based on practice type. However, because we did not include GP practices that primarily or exclusively treat skin cancer patients, it is unlikely that analysing the data based on practice type would have affected our outcome.

Strengths and weaknesses

This study consists of subgroup analyses of the results of a large cluster randomised clinical trial that was performed in a primary care setting. Thus, the study was not powered specifically for these analyses and the results should be interpreted with caution. As with all primary care studies of oncological problems, it was difficult to include a sufficient number of malignancies

to determine whether the observed difference is statistically significant. Nevertheless, our study included a higher proportion of malignant lesions than any previous study performed in a primary care setting, with an striking number of 22 melanomas.[4,7] Therefore, we believe that these analyses are relevant from a clinical point of view and provide an additional perspective regarding the influence of using dermoscopy to diagnose potentially malignant skin lesions in primary care.

Meaning of the study

This study revealed that using a dermoscope results in fewer benign lesions being either excised or referred to secondary healthcare. To date, this benefit has only been demonstrated for pigmented lesions.[2] In addition to the clear cost-saving benefit, this finding is also important for the patient as every excision (or biopsy) of a lesion carries potential risks such as inflammation, bleeding, and/or a cosmetically unappealing scar. Even though referral to secondary healthcare may involve less risks to the patient, the process itself can cause considerable stress, particularly among elderly patients. We hypothesise that the decreased number of interventions for benign lesions when using a dermoscope was caused, at least in part, by an increase in the confidence level of the GP, as was shown in a previous study.[2] On the other hand, three malignant lesions in the intervention group were handled using a watchful waiting approach. This might indicate that the presumed increase in confidence level might have coincided with a negative effect such as the GP overestimating his/her own diagnostic abilities. Thus, GPs should be careful not to overestimate their diagnostic abilities when using a dermoscope, and they should understand that using the dermoscope does not provide 100% diagnostic accuracy. However, a larger study with sufficient power that investigates the diagnostic confidence levels of GPs is needed to test these hypotheses.

Conclusions

Our results revealed that using a dermoscope has no significant effect on a GP's ability to accurately diagnose (pre)malignant lesions. However, our results did reveal that using a dermoscope resulted in fewer benign lesions being excised or biopsied and fewer patients with these lesions being referred to secondary healthcare. In addition, the probability of not receiving the required treatment for a malignant lesion seems to be low in both care as usual and dermoscopy groups. Although GPs should realise that the dermoscope is not perfect, we recommend that GPs use a dermoscope for diagnosing potentially malignant skin lesions.

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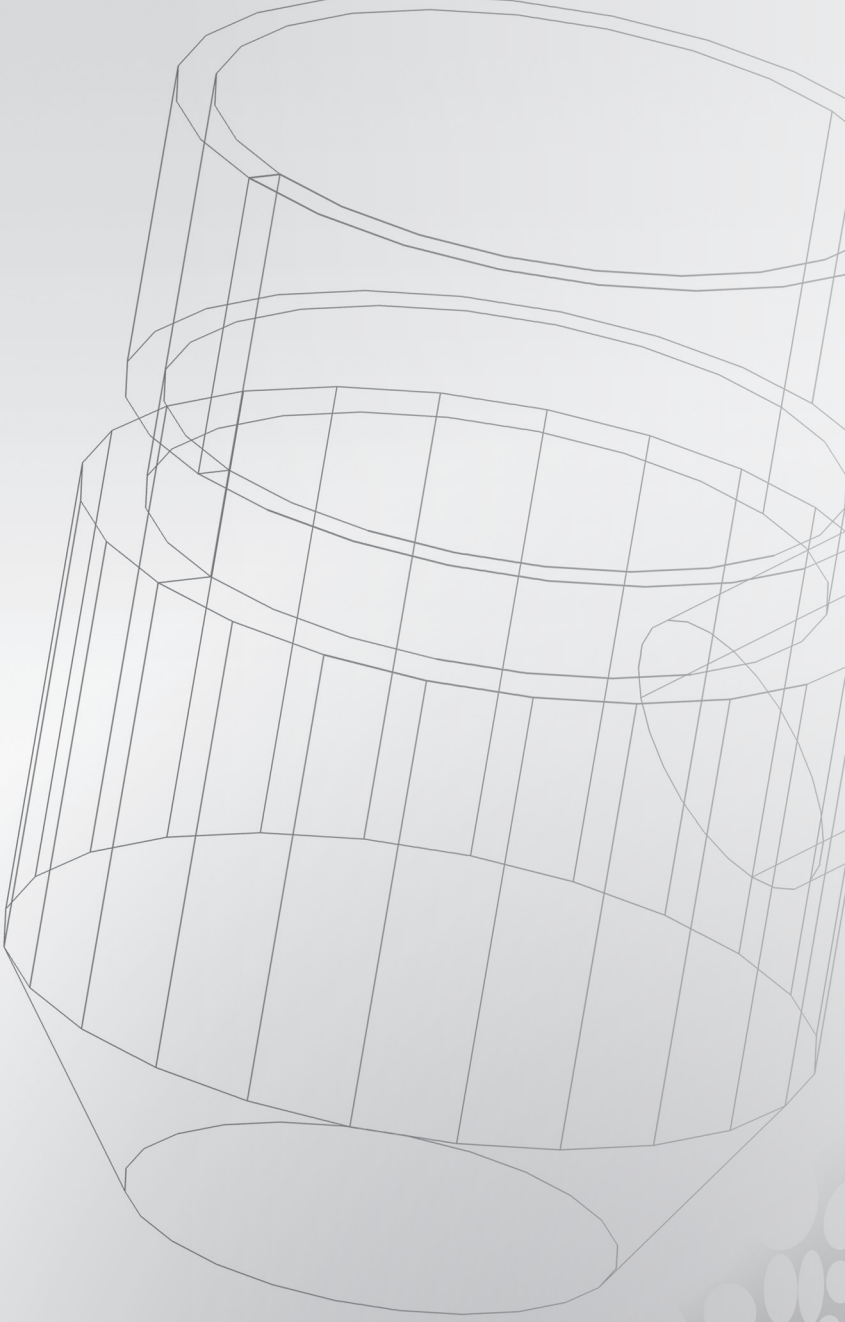

Chapter 6

Summary, general discussion, implications and conclusions

The ultimate goal of this thesis was to create an impetus for an improved and more evidence-based approach for diagnosing potentially malignant, pigmented and non-pigmented, skin lesions in general practice. To achieve this goal, we assessed the current state of potentially malignant skin lesions in general practice (the first aim of this thesis). In addition, we investigated the value of a diagnostic tool – the dermoscope – for the evaluation of potentially malignant skin lesions in general practice (the second aim of this thesis).

SUMMARY OF THE MAIN FINDINGS

The review in *Chapter 1* demonstrates that there is currently a lack of validated clinical decision aids and tools for examining and diagnosing potentially malignant skin lesions in general practice. Most of the studies performed to date were conducted in a secondary care setting and controlled clinical trials in primary care are scarce. This review also provides new directions for future areas of research.

In *Chapter 2*, the Registration Network Groningen was used to analyse the number of patients who visit their general practitioner (GP) due to a potentially malignant skin lesion. In addition, the outcome of those visits, e.g. referral, was examined. The analysis revealed that from 2001 through 2010, the number of consultations for potentially malignant skin lesions increased significantly by 6.8% per year. By 2010, an average GP practice saw seven potentially malignant skin lesions per week. Also, it was found that many of these potentially malignant skin lesions are either excised (29.5%) or referred to secondary care (14.3%).

Chapter 3 discusses the increasing number of skin tissue samples that both GPs and hospital specialists send to a large regional pathology laboratory. In addition, the results in this chapter reveal that the introduction of a financial incentive stimulated GPs to submit their skin tissue samples to the pathology laboratory, but did not change the ratio of benign/malignant lesions that were excised. So there seemed to be no widening of range of indication for excision. However, the number of submissions by hospital specialists did not decrease accordingly; thus no evidence to support substitution of care as a result of this incentive was demonstrated.

Based on a cluster randomised clinical trial, *Chapter 4* reports that the diagnostic accuracy of using a dermoscope is 10% higher than care as usual (OR 1.51, 95% CI: 0.96-2.37), although this effect was not statistically significant. On the other hand (and perhaps more important from a clinical perspective), the diagnostic accuracy for melanoma was 39% higher with the use of a dermoscope. Furthermore, the results reported in this chapter demonstrate that using a dermoscope for diagnosing potentially malignant skin lesions appears to be cost-effective.

In *Chapter 5*, we analysed further the cluster randomised clinical trial presented in Chapter 4. This additional analysis revealed no significant effect of using a dermoscope on the accuracy of diagnosing (pre)malignant lesions (OR 1.35, 95% CI: 0.52-3.54). However, the analysis revealed that in the intervention group (i.e. the dermoscopy group), three malignant lesions

– including one melanoma – were handled using a watchful waiting approach. In contrast, none of the malignant lesions in the control group (i.e. the care as usual group) were handled using a watchful waiting approach. On the other hand, the probability of incorrectly treating a (pre)malignant lesion seemed to be low for both the control and intervention group. Finally, the frequency of (perhaps unnecessarily) excising, biopsying or referring benign lesions to secondary care was reduced significantly with the use of a dermoscope.

GENERAL DISCUSSION

The motivation for the research presented in this thesis was the rather surprising fact that despite an increasing incidence of skin cancer and the gate-keeper role played by GPs in the Dutch healthcare system, remarkably little research has been performed regarding skin cancer in general practice. Moreover, a review of the clinical decision aids and tools available to the GP for diagnosing potentially malignant skin lesions revealed a lack of sufficiently validated clinical decision aids and tools for the examination of skin lesions for cancer in general practice.

The first aim of this thesis: 'To assess the current state of potentially malignant skin lesions in general practice.'

The reason for focusing on possible potentially malignant skin lesions – rather than on skin cancer – was that potentially malignant lesions are representative of what is commonly seen in general practice. A patient will not visit their GP with a skin cancer but they visit their GP because of a lesion which they suspect for malignancy. In fact, the majority of these suspect lesions are ultimately determined to be benign, and estimates suggest, although without direct evidence, that for each new case of skin cancer another 20-50 patients will consult their GP (or dermatologist).1 To achieve the first aim of this thesis, we needed to answer the following question: 'How often are potentially malignant skin lesions encountered in general practice, and with these patients?' The results reported in this thesis show that there is an increasing burden of these potentially malignant skin lesions in general practice. This increased burden was reflected by both the increasing number of consultations for these lesions and the increasing number of skin tissue samples that were submitted to a pathology laboratory from 2001 through 2010. By 2010, the average GP saw seven potentially malignant skin lesions each week, and this number has likely risen since 2010. Possible explanations for this increasing burden are the increasing incidence of skin cancer and an increased public awareness. The latter is likely due to the different number of public awareness campaigns that have emerged in recent years[2, 3] as well as increased attention from the media.

In addition, the study described in Chapter 2 showed that 29.5% of potentially malignant skin lesions in new patients are either excised or biopsied. However, the study described in Chapter 3 revealed that for every excised malignant lesion approximately seven benign lesions are

excised. Although some of these lesions might have been excised for cosmetic reasons, the majority were likely excised because the GP suspected that the lesion was malignant (or at the very least, was not convinced that it was benign). Even though the ratio of benign/malignant lesions was lower than reported in other studies[4-6], in most cases the lesion was benign and probably did not need to be excised for medical reasons. Additionally, 14.3% of potentially malignant skin lesions in new patients are referred to secondary healthcare. A previous study reported that the sensitivity and specificity of referral accuracy of GPs for patients with skin tumours was 54.1% and 71.3% respectively when using care as usual.[7] In conclusion, the burden that potentially malignant skin lesions places on general practice is increasing, and many patients are either referred to secondary healthcare or have their lesions excised or biopsied. Both referral and excision accuracy – and therefore diagnostic accuracy – have room for improvement.

The second aim of this thesis: 'To investigate the value of a diagnostic tool – the dermoscope - for the evaluation of potentially malignant skin lesions in general practice.'

Although there is currently a lack of sufficiently validated tools for examining potentially malignant skin lesions in general practice, two studies have reported that using a dermoscope improved diagnostic sensitivity for melanoma in a primary care setting.[8, 9] Furthermore, using a dermoscope improved referral accuracy and this study additionally reported that non-melanoma skin cancers were diagnosed more accurately using a dermoscope.[7] In Chapters 4 and 5, the dermoscope was studied as a tool for diagnosing all, both pigmented and non-pigmented, skin lesions in general practice. These studies revealed that the use of a dermoscope by GPs, after formal training, does not decrease the sensitivity for detecting melanoma. This is in contrast to the decreased sensitivity that was reported for untrained dermatologists.[10] In fact, although not statistically significant, the use of a dermoscope lead to a 10% higher diagnostic accuracy, with significantly less benign lesions being excised, biopsied or referred to secondary care. We also found an apparent increase in diagnostic accuracy for melanoma. These findings are consistent with other studies performed in primary care.[7-9] On the other hand, it should be noted that in the dermoscopy group three malignancies (one of which was a melanoma) were handled using a watchful waiting approach. In contrast, no malignant lesions were handled with a watchful waiting approach in the control group. This finding may indicate that although there is a trend towards improved diagnostic accuracy using dermoscopy for all potentially malignant lesions (including melanomas), dermoscopy might also cause GPs to overestimate their own diagnostic accuracy. This overconfidence could possibly lead to a poorer outcome if the lesion is diagnosed incorrectly as benign. On the other hand, the likelihood of incorrectly treating a malignant or pre-malignant lesion seems to be low both with and without the use of a dermoscope. Another element in our

study of dermoscopy in general practice was to assess its cost-effectiveness, as this has never been studied previously. Our results demonstrate that the dermoscope appears to be a cost-effective intervention. In conclusion, the dermoscope seems to be a valuable diagnostic tool available to the GP for investigating and diagnosing potentially malignant skin lesions. However, GPs must understand and account for the fact that also the dermoscope is not perfect.

STRENGTHS AND WEAKNESSES OF THIS THESIS

The strengths and weaknesses of the individual studies included in this thesis have been described in the corresponding chapters. However, the major overall strength of the studies in this thesis is also a weakness. Most of the studies were performed on potentially malignant skin lesions that were presented to a GP. Unfortunately, it is difficult to define 'potentially malignant', particularly in a registry study, as 'potentially malignant' must be defined retrospectively. This may have led to either an overestimation or an underestimation of the actual number of potentially malignant skin lesions. Nonetheless, these potentially malignant skin lesions are a reflection of a GP's daily practice. Furthermore, a diagnostic tool such as a dermoscope will mainly be used on potentially malignant skin lesions instead of skin cancer and most will ultimately be determined to be benign. Therefore, studying potentially malignant skin lesions provides a valuable insight into the growing burden that the skin cancer epidemic places on general practitioners.

IMPLICATIONS FOR EDUCATION, CLINICAL PRACTICE AND RESEARCH

First of all, the results presented in this thesis show that given the high number of consultations for potentially malignant skin lesions, the low diagnostic accuracy and the high number of benign lesions that are either excised or referred to secondary healthcare, GPs clearly need further training . Because many GPs lack a proper training in dermatology,[11, 12] this training should be incorporated into the standard educational programme of GP registrars. In addition, for an immediate effect also training programs for currently practising GPs are needed. Furthermore, the current Dutch national guidelines regarding skin cancer were not developed for GPs and no GP was involved in developing these guidelines. Moreover, these guidelines primarily address treatment rather than the diagnostic pathway.[13-15] Therefore, developing a guideline ('NGH standaard') regarding potentially malignant skin lesions will further increase diagnostic, referral and excision accuracy. Such a guideline could be modelled after the NHG standaard for Bacterial Skin Infections, which provides an overview of several skin infections together with their corresponding efflorescences and treatment advice.[16] For further improvement of the diagnostic accuracy, after receiving formal training, GPs should

be advised to use a dermoscope to examine potentially malignant skin lesions. However, GPs should also understand that the dermoscope is not perfect from a diagnostic perspective.
Based on the findings presented in this thesis, several areas of future research can be identified. Some of these were already discussed in the review presented in Chapter 1 and will not be repeated here. Given the first aim of this thesis, one might ask, '*Do GPs find the increasing burden of potentially malignant skin lesions to be truly a burden, and if so, what would help to reduce this burden for the GP?*' Perhaps there is currently a need – or will be in the future – for someone to take over these consultations, at least in part (for example, a nurse practitioner who specialises in potentially malignant skin lesions). In addition, one might ask, *'Why do these patients visit their GP, and can we decrease the number of consultations without discouraging patients with skin cancers to visit their GP?'* Finally, qualitative research might answer the question, '*Why are so many lesions referred to secondary healthcare or excised?*' Is this due solely to insecurity on the part of the GP, or is this significantly influenced by cosmetic reasons? Finding answers to these questions will provide better insight into potentially malignant skin lesions in general practice and will therefore reveal areas that can be improved to ultimately decrease the number of unnecessary consultations, excisions and referrals to secondary healthcare. This is highly relevant to patients (who will experience fewer excisions and referrals), GPs (who will be able to spend more time on other tasks), secondary caregivers (who will receive fewer unnecessary referrals), and society as a whole (as less money will be spent on consultations and excisions).
The first obvious implication for future research that stems from the second aim of this thesis is *'to evaluate the actual added value of using a dermoscope with a sufficiently large sample size'*. In such a study, it is important to also look at the treatment given to false negative lesions (i.e. malignant lesions that are not diagnosed as malignant) and to examine the confidence levels of the GPs. Furthermore, because increasing one's experience with dermoscopy influences diagnostic accuracy,10 it would be interesting to ask, *'Does the frequency of using a dermoscope affect diagnostic accuracy in general practice?'* If so, this might suggest that rather than training every GP to use a dermoscope, only one GP per practice – or region – should be trained. Thus providing that a GP using a dermoscope will acquire, and also maintain, sufficient experience with this diagnostic tool.

GENERAL CONCLUSIONS

Overall this thesis shows that an increasing number of potentially malignant skin lesions are being seen in general practice and many of these lesions are excised (or biopsied) or referred to secondary care. Although not perfect, the dermoscope seems to be a valuable tool for diagnosing these lesions. Furthermore, the results presented in this thesis shed light on the need to educate GPs and develop a guideline specifically for potentially malignant skin lesions. Additionally, this thesis provides a roadmap for future research.

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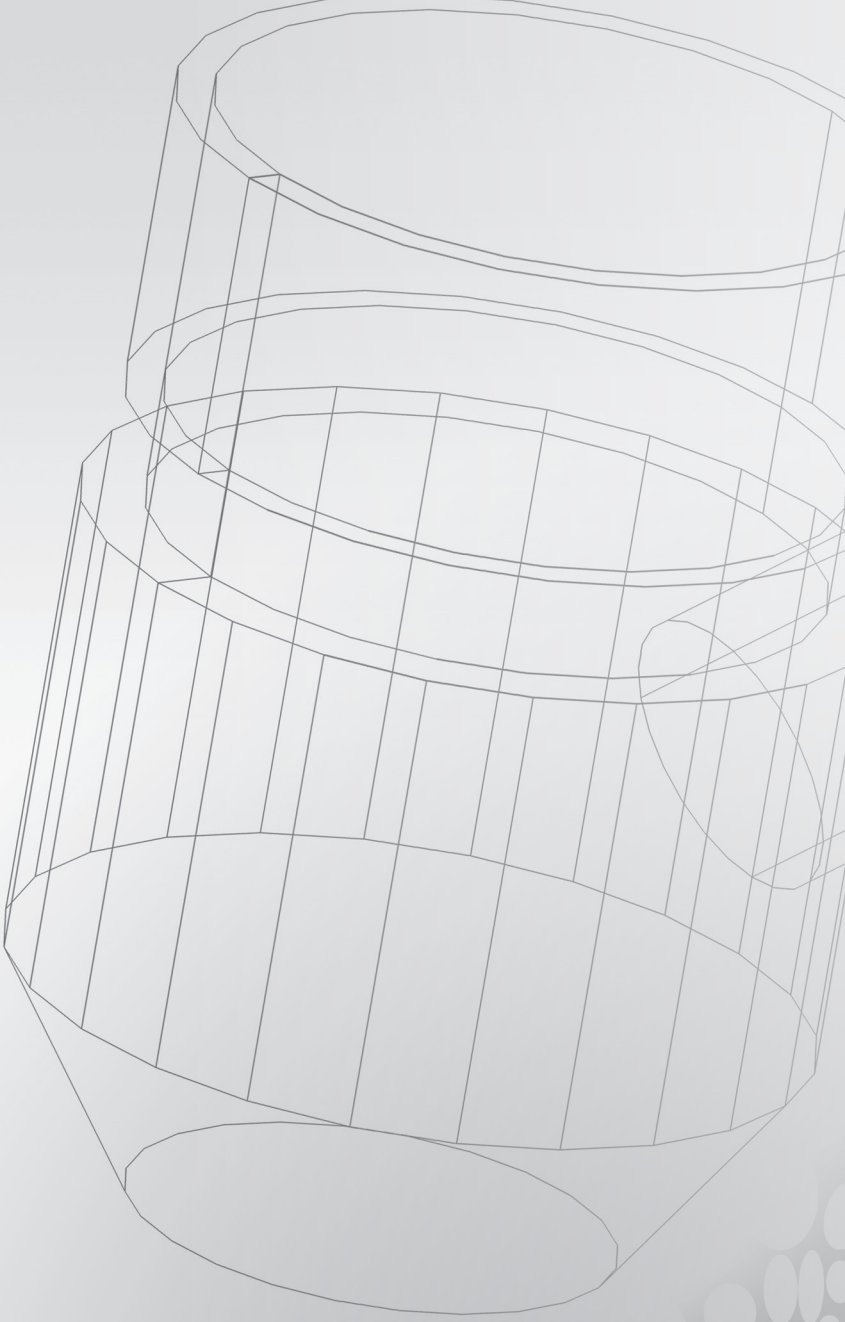


Chapter 7

Nederlandse samenvatting

INLEIDING EN DOELSTELLING

Huidkanker komt steeds vaker voor, met name door een toegenomen blootstelling aan zonlicht. Volgens huidige schattingen krijgt één op de zes Nederlanders op een zeker moment huidkanker. De meest voorkomende soorten huidkanker zijn het melanoom, het plaveiselcelcarcinoom en het basaalcelcarcinoom. De prognose voor iemand met huidkanker is sterk afhankelijk van het soort en het stadium waarin de kanker zich bevindt. Basaalcelcarcinomen en in mindere mate ook plaveiselcelcarcinomen zaaien vrijwel nooit uit en leiden daardoor zelden tot de dood. Toch kunnen deze huidkankers, met name bij late ontdekking, leiden tot forse lokale schade aan het omliggende weefsel. Het melanoom zaait vaker uit, maar is in een vroeg stadium goed te behandelen. Is het melanoom al in een vergevorderd stadium (stadium IV) dan is na 5 jaar nog slechts 15-20% van de patiënten in leven. Daarom is het van groot belang dat huidkanker tijdig wordt gediagnostiseerd en behandeld.

In Nederland komen de meeste patiënten met een huidplekje dat zij niet vertrouwen eerst bij de huisarts. De huisarts zal dan enkele vragen stellen, de anamnese, om vervolgens het plekje te onderzoeken. Afhankelijk van de diagnose zal de huisarts er voor kiezen om een afwachtend beleid te volgen, het plekje zelf weg te halen of de patiënt te verwijzen naar een specialist in het ziekenhuis. Meestal is dit een dermatoloog of (plastisch) chirurg. In het geval van huidkanker is het afhankelijk van het soort en het stadium of de patiënt daarna onder controle blijft van de behandelend arts.

Hoewel vrijwel elke patiënt eerst door de huisarts wordt gezien blijkt (*hoofdstuk 1*) dat de huisarts weinig tot geen gevalideerde handvaten heeft voor het onderzoeken van verdachte plekjes. Daarnaast is er in de opleiding tot (huis)arts weinig aandacht voor deze veelvoorkomende, mogelijk maligne (kwaadaardige) huidafwijkingen en voelen huisartsen zich onzeker over hun kunde om deze plekjes te diagnosticeren.

Het hoofddoel van dit proefschrift was een aanzet te geven tot een verbeterde en meer wetenschappelijk onderbouwde diagnostiek van deze verdachte plekjes. Voor het bereiken van dit hoofddoel zijn twee doelstellingen onderzocht. De eerste doelstelling was het vaststellen van de huidige stand van zaken van deze verdachte plekjes in de huisartspraktijk. Hoe vaak presenteren patiënten zich met een verdachte huidafwijking bij de huisarts en wat gebeurt er mee? De tweede doelstelling was om de toegevoegde waarde van een diagnostisch hulpmiddel voor het onderzoek van verdachte plekjes, de dermatoscoop, te onderzoeken in de huisartspraktijk. Deze dermatoscoop is een soort vergrootglas waarmee men door de bovenste laag van de huid heen kan kijken. Hierdoor worden structuren gezien die normaal met het blote oog niet waarneembaar zijn. We weten dat de dermatoscoop dermatologen helpt om verdachte plekjes beter te diagnosticeren, maar of dat ook voor huisartsen geldt, was nog niet goed onderzocht.

SAMENVATTING VAN DE HOOFDSTUKKEN

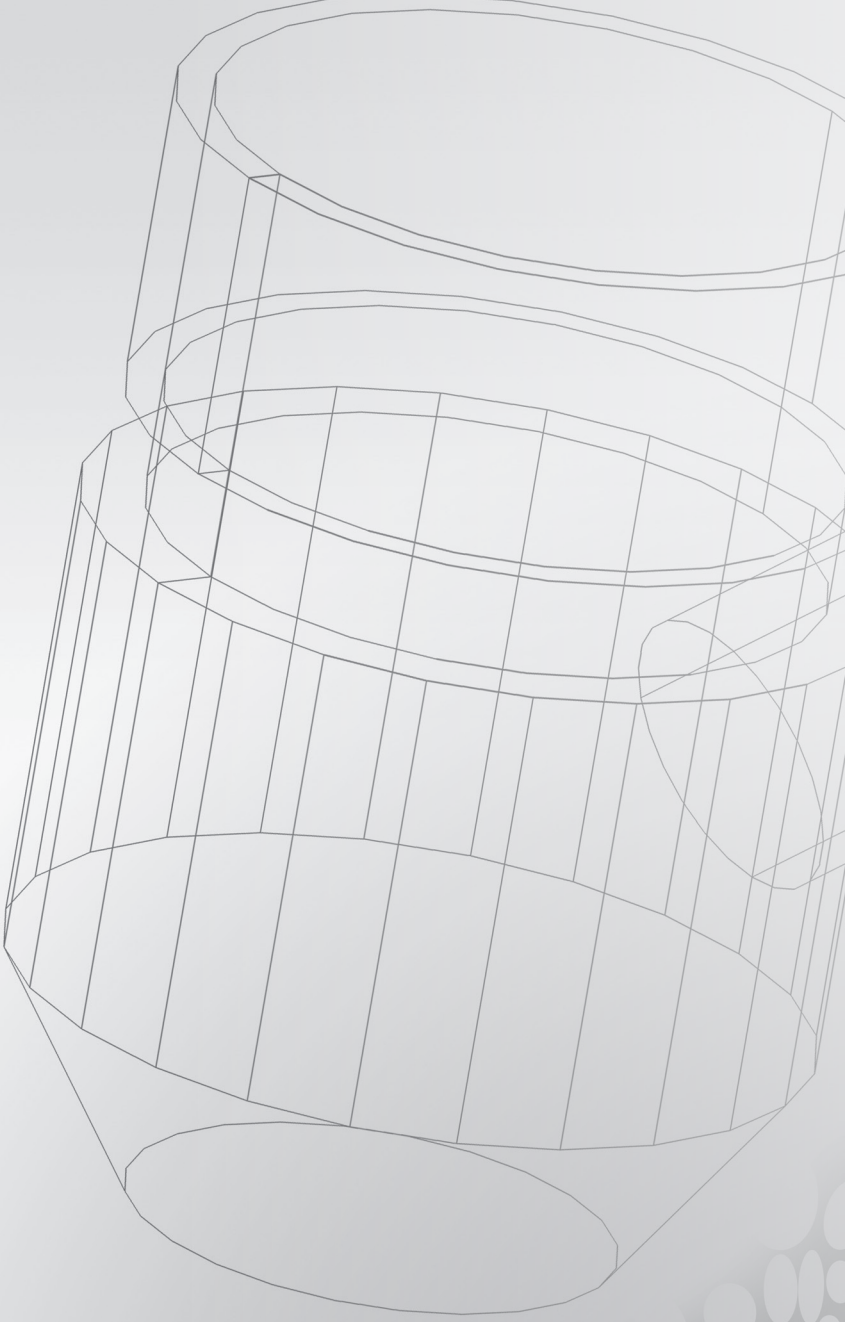
In *hoofdstuk 1* wordt een achtergrond geschetst zoals die ook hierboven kort beschreven is. Tevens geeft de review die gepresenteerd wordt in dit hoofdstuk, naast de conclusie over een gebrek aan gevalideerde algoritmen en instrumenten, richting aan toekomstig onderzoek. De uitkomsten van deze onderzoeken zouden moeten leiden tot een verbetering van de diagnostiek van verdachte plekjes.
Hoofdstuk 2 beschrijft de huidige stand van zaken en de ontwikkelingen in de afgelopen 10 jaar van verdachte plekjes in de huisartspraktijk. Met behulp van een database gebaseerd op de registraties van huisartsen, is er onderzocht hoe vaak een huisarts wordt geconsulteerd voor verdachte plekjes en ook wat hier vervolgens mee gebeurt. Hieruit blijkt dat de huisarts in toenemende mate wordt geconsulteerd voor verdachte plekjes. Op dit moment ziet de huisarts er gemiddeld 7 per week. Verder blijkt dat bij nieuwe verdachte plekjes bij een groot deel van de patiënten het plekje wordt weggesneden (excisie, 29,5%) of dat de patiënt wordt verwezen naar een specialist in het ziekenhuis (14,3%).
Een andere invalshoek om te kijken naar hoe vaak verdachte plekjes in de afgelopen 10 jaar voorkwamen en wat er mee gebeurde wordt gebruikt in *hoofdstuk 3*. Hiervoor wordt gekeken in een database van een pathologisch laboratorium. Hierin staan alle huidinzendingen van zowel huisartsen als specialisten. Analyse van deze inzendingen laat zien dat er in de afgelopen 10 jaar een stijgende lijn te zien is voor het aantal inzendingen van zowel huisartsen als ziekenhuis specialisten. Tevens blijkt dat na de invoering (in 2006) van een financiële stimulans voor huisartsen om zelf plekjes te gaan wegsnijden deze toename nog groter is geworden. De verwachting was dat dit zou leiden tot een verschuiving van een deel van de excisies van ziekenhuis specialisten naar huisartsen, maar dit kon niet worden aangetoond in dit onderzoek. Toch lijkt de drempel voor huisartsen om benigne (goedaardige) afwijkingen weg te gaan snijden niet verlaagd. De verhouding tussen weggesneden benigne afwijkingen en maligne afwijkingen bleef namelijk gelijk (7 benigne afwijkingen : 1 maligne afwijking).
Op basis van *hoofdstuk 2* en *hoofdstuk 3* blijkt dat er veel actie zoals excisies en verwijzingen, wordt ondernomen op deze verdachte plekjes hoewel een groot deel hiervan benigne is. Immers voor elke maligne afwijking worden er 7 benigne afwijkingen weggesneden. Een verbetering van de diagnostiek zou het aantal excisies en verwijzingen naar een specialist in het ziekenhuis moeten kunnen verlagen.
In *hoofdstuk 4* is onderzocht in hoeverre een dermatoscoop bijdraagt aan de diagnostiek van verdachte plekjes in de huisartspraktijk. Hiertoe is de diagnostische accuratesse, dat is het percentage juist gediagnostiseerde verdachte plekjes, met en zonder dermatoscoop onderzocht met behulp van een cluster gerandomiseerde studie. Voor deze studie werden de huisartspraktijken willekeurig ingedeeld in de controle groep die de patiënten onderzocht zoals gewoonlijk of in de interventiegroep die de patiënten onderzocht zoals gewoonlijk én met dermatoscoop. De huisartsen die meededen aan dit onderzoek kregen eerst scholing

in de diagnostiek van verdachte plekjes en de huisartsen die ook de dermatoscoop gingen gebruiken kregen daarnaast nog een cursus dermatoscopie. Vervolgens hebben de huisartsen ruim een jaar lang patiënten geïncludeerd die op het spreekuur kwamen met een verdacht plekje. Uit deze studie kwamen de volgende resultaten en conclusies naar voren: ondanks dat de dermatoscoop de diagnostische accuratesse met 10% verhoogt tot 50.5% is dit verschil niet significant. Daarnaast, en wellicht is dit nog wel belangrijker, blijkt dat het percentage juist gediagnostiseerde melanomen bijna 3x zo hoog was met het gebruik van een dermatoscoop. Hier dient wel de kanttekening te worden gemaakt dat dit was gebaseerd op slechts 22 melanomen. Tot slot lijkt de dermatoscoop een kosteneffectieve interventie. Er zijn nauwelijks extra kosten verbonden aan het gebruik van de dermatoscoop terwijl er een grote kans is op effectiviteit.

Hoofdstuk 5 is gebaseerd op de resultaten van de studie beschreven in hoofdstuk 4. Het blijkt dat het gebruik van de dermatoscoop geen invloed heeft op de juistheid van de diagnostiek (sensitiviteit en specificiteit) van (pre)maligne afwijkingen. Wel zijn er in de interventiegroep 3 maligniteiten met een afwachtend beleid behandeld terwijl dit met geen enkele maligniteit is gebeurd in de controle groep. Vanwege het kleine aantal kan er geen uitspraak worden gedaan over de invloed van het gebruik van de dermatoscoop, maar het lijkt goed om te realiseren dat ook de dermatoscoop niet feilloos is. Van de andere kant blijkt dat benigne afwijkingen een betere behandeling krijgen, dat is een afwachtend beleid, in de interventiegroep dan in de controle groep.

CONCLUSIE

Op basis van dit proefschrift kan worden geconcludeerd dat huisartsen in toenemende mate worden geconsulteerd voor verdachte plekjes. Veel van deze verdachte plekjes worden weggesneden door de huisarts of de patiënt wordt verwezen naar een specialist in het ziekenhuis. De diagnostiek door de huisarts laat dan ook nog ruimte voor verbetering. De dermatoscoop, hoewel niet feilloos, lijkt hiervoor als diagnostisch instrument een waardevolle toevoeging te zijn voor de huisarts.



Dankwoord

DANKWOORD

En dan tot slot het populairste hoofdstuk van dit boek, het dankwoord. Veel mensen zijn betrokken geweest bij het tot stand komen van dit proefschrift. Een aantal van hen wil ik hier bedanken voor hun bijdrage en alles wat zij voor mij betekend hebben.

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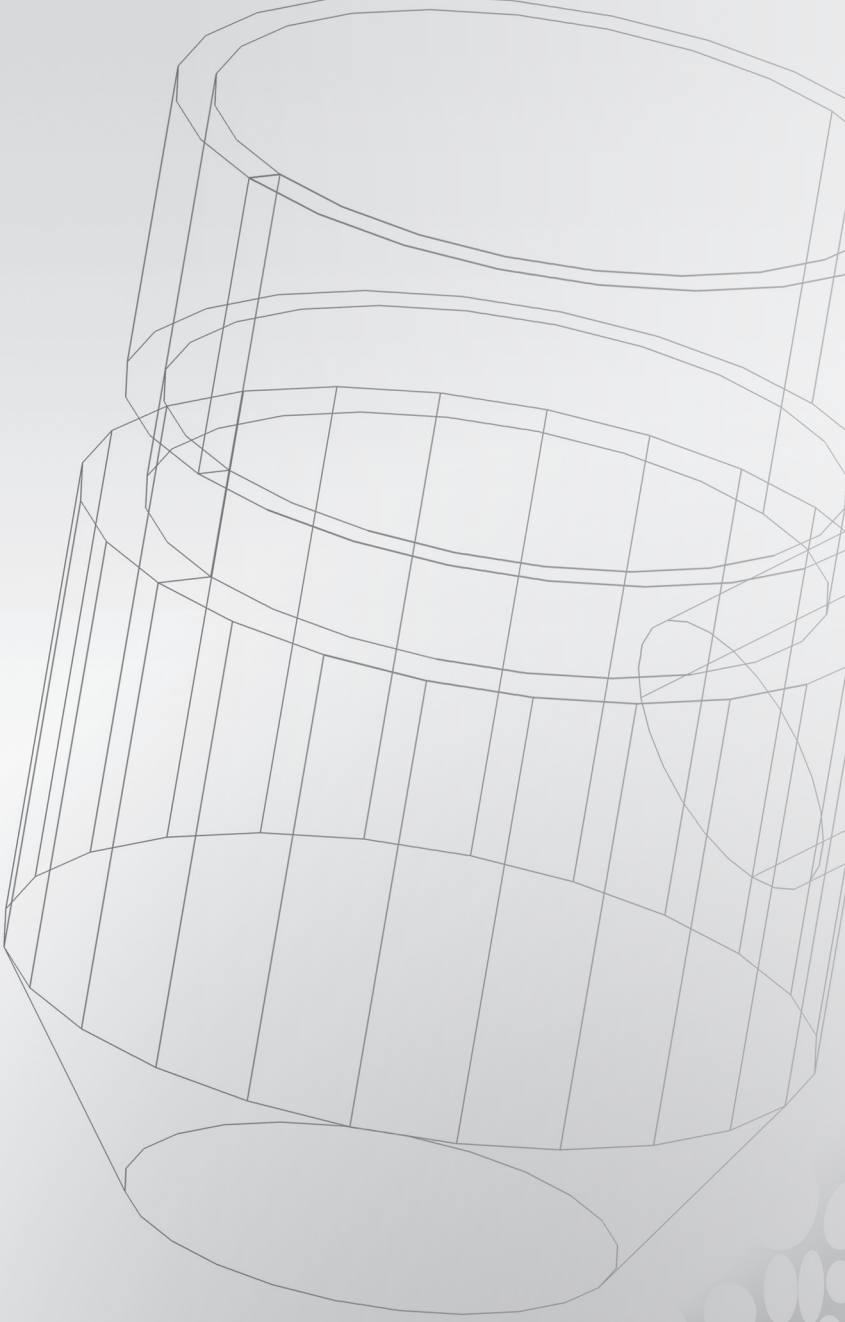

About the author

ABOUT THE AUTHOR

Cecile Johanne Louise Koelink was born on March the 28th in 1983 in 's Hertogenbosch, the Netherlands. In 2001 she graduated from secondary school (Maartenscollege Haren) and started to study Biology at the University of Groningen. After passing her propaedeutic examination in Biology she started to study medicine, also at the University of Groningen. During these studies her interest in scientific research grew. This led to a research on Tyrosinemia Type I, a rare metabolic disease. Also, she attended the Scientific Research Week of the Junior Scientific Masterclass. After graduating in medicine and receiving her medical doctor degree (MD) in 2008, she started her PhD research on diagnosing skin cancer in general practice combined with the specialist training for general practitioner (AIOTHO). Her PhD research resulted in this thesis under the supervision of Prof. Dr. K. van der Meer, Prof. Dr. M.F. Jonkman and Dr. W.K. van der Heide and she expects to be a general practitioner by the beginning of 2015.

She lives together with her husband Philippe and her daughters and son Heleen, Evert and Dorien.